UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

GRÜNENTHAL GMBH, and DEPOMED, INC. Plaintiffs/Counterclaim Defendants, v. ACTAVIS ELIZABETH LLC, ALKEM LABORATORIES LIMITED, and ROXANE LABORATORIES, INC., Defendant/Counterclaim Plaintiff.	Civil Action No. 2:14-cv-04507-CCC-MF **HIGHLY CONFIDENTIAL – FILED UNDER SEAL**
AND CONSOLIDATED CASES	Civil Action No. 2:13-cv-06929-CCC-MF Civil Action No. 2:14-cv-07803-CCC-MF Civil Action No. 2:14-cv-03941-CCC-MF Civil Action No. 2:14-cv-04617-CCC-MF Civil Action No. 2:14-cv-06797-CCC-MF

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Defendants' Proposed Findings of Fact

Regarding U.S. Patent Nos. RE39,593, 7,994,364, and 8,536,130

I. U.S. PATENT RE39,593

A. Chemical Obviousness of the Asserted Claims Under 35 U.S.C. § 103

1. U.S. Patent No. RE39,593 ("the '593 patent") issued on April 24, 2007 as a reissue of U.S. Patent No. 6,248,737 (DTX-752), and has an earliest application filing date of July 23, 1994. DTX-1346 at Front Page.

2. Patent and printed publications dated before July 23, 1994 qualify as prior art to the '593 patent under either 35 U.S.C. ¶¶102(a) or 102(b). 3.16.16 Martin Tr. 178:8-18.

3. Plaintiffs have asserted claims 8, 61, 117 and 147 of the '593 patent against Defendants. 3.16.16 Martin Tr. 178:22-181:4.

4. The Court qualified Professor Stephen F. Martin, Ph.D., the M. June and J. Virgil Waggoner Regents Chair in Chemistry at the University of Texas, as an expert in organic and medicinal chemistry, including the study of structure activity relationships and the design and synthesis of pharmaceutically active compounds, including analgesics. 3.16.16 Martin Tr. 176:24-177:18.

5. Professor Martin has experience in my experience is in synthetic organic, bio-organic, and medicinal chemistry. He has extensive experience in the design, synthesis, and optimization of small molecules that bind to biological targets, especially proteins. The research group he leads at the University of Texas has been involved in methods and synthesis of compounds that are biologically active, and in that context, he has studied structure-activity relationships ("SAR") and has worked on compounds that have various activities including pain. 3.16.16 Martin Tr. 166:1-12; 168:3-169:17.

6. Professor Martin has published over 320 publications in refereed journals, he has consulted with several major pharmaceutical companies on drug discovery, including Abbott, Pfizer and Merck; he is an editor of several journals in organic chemistry including editor for Tetrahedron of the Americas and "Organic Synthesis; and he has been awarded several honors, including the Alexander von Humbolt Prize, and NIH Career Development Award and the ACS Arthur C. Cope Scholar Award. 3.16.16 Martin Tr. 169:18-179:15.

1. **The Person of Ordinary Skill in the Art (POSITA)**

7. With respect to the '593 patent, a POSITA would have had education and/or experience in a field related to the design and synthesis of new analgesic compounds, including the fields of organic chemistry, medicinal chemistry and pharmacology, and knowledge of the scientific literature concerning the same, specifically the design and synthesis of organic compounds used for the treatment of pain, including opioid analgesic and opioid analogs for the treatment of pain as of July 1994. The education and experience levels of a POSITA would be a person holding a Ph.D. and having 3–5 years of experience in the design and synthesis of analgesics, including opioid analgesics. 3.16.16 Martin Tr. 181:20-183:8.

8. Professor arrived at his opinions regarding obviousness of the asserted claims of the '593 patent using the above definition of a POSITA, but his opinions would not change if the Court were to adopt a definition of a POSITA which included a bachelor's degree instead of a Ph.D. 3.16.16 Martin Tr. 183:9-25.

2. **The Prior Art Would Have Motivated a POSITA to Select Tramadol or O-Desmethyltramadol as Lead Compounds**

9. In selecting a lead compound for further development of an improved analgesic a POSITA would familiarize themselves with all different kinds of compounds that had analgesic activity, look at properties, including side effects, and consider in general all the things that were

known about those different compounds, and then they would make judgments on what they thought might be a good starting point. 3.16.16 Martin Tr. 187:21-188:11.

10. Among the various known analgesics in 1994, a POSITA would consider opioids, non-steroidal anti-inflammatory compounds (NSAIDs), monoamine uptake inhibitors, cannabinoids, as well as compounds with more than one of these activities, so-called compounds with polypharmacology. 3.16.16 Martin Tr. 189:7-190:22.

11. Professor Martin, Plaintiffs' expert Dr. Roush and inventor Helmut Buschmann all agree that the only analgesic compound known in 1994 to possess both opioid and non-opioid activities is tramadol. 3.16.16 Martin Tr. 190:23-192:19; 3.22.16 Roush Tr. 57:12-16; 58:11-14; 161:13-20; 3.10.16 Buschmann Tr. 89:14-90:3.

12. A POSITA would have known by 1994 that tramadol was an approved analgesic in Europe and had been described as safe and effective in the literature based on clinical trials in humans, as admitted by Plaintiffs' expert Dr. Roush. DTX-2059; DTX-2060; 3.22.16 Roush Tr. 66:5-71:15. Tramadol was first patented in the U.S. in 1972. DTX-746.

13. As the patent life on tramadol was expiring in the late 1980's and early-1990's, Grünenthal initiated its "Tramadol Successor Project" to develop a next-generation tramadol analog which maintained tramadol's unique mixed opioid/non-opioid mechanism of action and retained the key chemical structure of tramadol responsible for its analgesic action. DTX-1027 (Tramadol Successor Brochure – English Version).

14. Plaintiffs' expert Dr. Roush gave his initial opinion that tramadol would not be considered in the top tier of prior art compounds in July 1994 because it was not approved by the U.S. FDA at that time, but later admitted that he did not know if the approval standards differed in Europe and the U.S. and hadn't considered how his opinion would have created a different

standard of obviousness for a POSITA working in the U.S. than for those working in Europe or other parts of the world. 3.22.16 Roush Tr. 63:17-66:4.

15. Raffa, R. B., et al., "Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an '***atypical***' opioid analgesic," *J. Pharmacol. Exp. Ther.*, 260:275-285 (1992) ("*Raffa I*"), was published in 1992, and qualifies as prior art to the claims of the '593 patent under 35 U.S.C. § 102(b). DTX-866 (emphasis added).

16. *Raffa I* teaches that "[t]hese results suggest that tramadol-induced antinociception is mediated by opioid (μ) and nonopioid (inhibition of monoamine uptake) mechanisms." DTX-866 at 1 (Abstract).

17. According to *Raffa I*, "[t]ramadol hydrochloride, (1RS,2RS)-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl)-cyclohexanol HCl (fig. 1), is an orally active, clinically effective, centrally acting opioid analgesic. In acute therapeutic use it has analgesic efficacy and potency comparable to those of codeine, pentazocine or dextropropoxyphene." DTX-866 at 1.

18. *Raffa I* further notes that "[t]aken together, the data suggest that tramadol produces antinociception *via* an opioid (predominantly μ) mechanism and also *via* a separate nonopioid mechanism (probably related to its ability to inhibit neuronal uptake of norepinephrine or serotonin). Both mechanisms contribute to antinociception *in vivo*. Hence, the ***atypical nature of the clinical analgesic activity of tramadol apparently derives from the combined contributions of an opioid and nonopioid component***, without a similarly interactive combination of side effects." DTX-866 at 10 (emphasis added).

19. "The ability of tramadol to inhibit the neuronal uptake of monoamines in the same concentration range at which it binds to Mu-opioid receptors is ***quite distin***ct from the results for

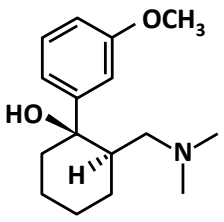
morphine or codeine and ***clearly differentiate tramadol from these 'typical' opioids.***" DTX-866 at 4 (emphasis added).

20. A POSITA would have been motivated to start with tramadol as a lead compound because of its unique combination of opioid and non-opioid activities, which was known to provide strong analgesia without the side effects of pure opioids.

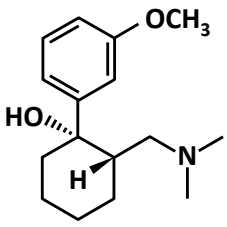
> So I think the important message here is that tramadol is unique, it has this dual mode of action, it's got opioid and nonopioid mechanisms of action, and because it has a dual mode of action, we can tone down how much we use the opioid part of it for our analgesic effect because we can use a combination of two different things, and because we can tone down the opioid part of the equation, it means that we don't have some of the side effects, at least certainly not to the same degree as we have in the opioid analgesics, and that's a big plus, because one of the huge negatives of all of these opioids is, are there side effects, and if you have a compound that certainly has minimal or no side effects, no significant side effects, as this passage says, that's pretty impressive.

3.16.16 Martin Tr. 194:25-195:13.

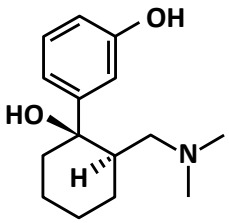
21. Tramadol is a mixture of two enantiomers and it is metabolized to a mixture of two enantiomers of *O*-desmethyltramadol (ODMT).



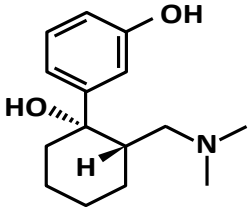
R,R-Tramadol



S,S-Tramadol



R,R-ODMT



S,S-ODMT

3.16.16 Martin Tr. 197:8-200:6.

22. The tramadol mixture of enantiomers, the ODMT mixture of enantiomers and each of the four individual compounds were studied in the prior art for their analgesic activity. 3.16.16 Martin Tr. 200:12-24.

23. Hennies, H.-H., et al., "Receptor binding, analgesic and antitussive potency of tramadol and other selected opioids," *Arzneim-Forsch. Drug Res.*, 38:877-880 (1988) (*Hennies*"), was published in 1988, and qualifies as prior art to the claims of the '593 patent under 35 U.S.C. § 102(b). DTX-691.

24. *Hennies* describes the hydrochloride salt of O-desmethyltramadol and tramadol. *Id.* at 2.

25. At Table 2, *Hennies* also shows that the analgesic effect of O-desmethyltramadol is approximately three times greater than the analgesic effect of tramadol:

Table 2: ED_{50}-values (mg/kg) of analgesic and antitussive effects in conscious rats 10 min after i.v. application (confidence limits in parantheses). Ratio of antitussive to analgesic potency was calculated by dividing ED_{50}-value of tail flick by ED_{50}-value of cough inhibition.

Compound	Analgesic effect	Antitussive effect	Ratio
O-Desmethyltramadol	2.94 (2.03—4.26)	4.31 (30.5—6.87)	0.68
Tramadol	8.97 (6.20—13.0)	3.52 (2.68—4.74)	2.55
Morphine	1.37 (0.80—2.34)	3.89 (2.72—6.03)	0.35
Codeine	8.60 (5.76—12.8)	13.0 (8.66—28.0)	0.66
Hydromorphone	0.28 (0.20—0.38)	0.29 (0.23—0.35)	0.97
Hydrocodone	1.18 (0.75—1.85)	1.87 (1.47—2.30)	0.66

*Id.*at 3.

26. The take-home message from *Hennies* is that ODMT is a better analgesic than tramadol. 3.16.16 Martin Tr. 209:12-25; 221:2-7.

27. Driessen, B., et al., "Interaction of the central analgesic, tramadol, with the uptake and release of 5-hydroxytryptamine in the rat brain *in vitro*." *British J. Pharmacol.*, 105:147-151

(1992) ("*Driessen I*"), was published in 1992, and qualifies as prior art to the claims of the '593 patent under 35 U.S.C. § 102(b). DTX-758.

28. *Driessen I* states that "[t]ramadol is a centrally acting analgesic with low opioid receptor affinity." *Driessen I* also states that "[t]ramadol inhibited the uptake of [^{3}H]-5-HT into purified rat frontal cortex synaptosomes with an IC_{50} of 3.1 μM. The (+)-enantiomer was about four times more potent than the (–)-enantiomer; the main metabolite of tramadol, O-desmethyltramadol, was about ten times less potent." *Id.* at 1 (Abstract).

29. A POSITA would understand from the teachings of *Driessen I* that ODMT has weaker interactions with serotonin reuptake system and would like have fewer serotonin-related side effects than tramadol. 3.16.16 Martin Tr. 211:18-25; 221:8-14.

30. Driessen, B., et al., "Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro," *British J. Pharmacol*., 108:806–811 (1993) ("*Driessen II*"), was published in March 1993, and qualifies as prior art to the claims of the '593 patent under 35 U.S.C. § 102(b). DTX-694.

31. According to *Driessen II*, "[t]ramadol inhibited the uptake of [^{3}H]-noradrenaline into purified rat hypothalamic synaptosomes with an IC_{50} of 2.8 μM; the (–)-enantiomer was about ten times more potent than the (+)-enantiomer. Results with the principal metabolite O-desmethyltramadol were very similar." *Id.* at 1 (Abstract). *Driessen II* also states that "[t]he interaction with the noradrenaline transporter is stereoselective." *Id.*

32. A POSITA would understand form the teachings of *Driessen II* that the (-)-enantiomers of both tramadol and ODMT are more potent in binding to the noradrenaline receptor than the (+)-enantiomers. 3.16.16 Martin Tr. 212:5-214:17; 221:15-17.

33. Raffa *et al.,* "Complementary and Synergistic Antinociceptive Interaction between the Enantiomers of Tramadol," *J. Pharmacol. Exp. Ther.*, 267(1):331-340 (1993) ("*Raffa II*"), was published in October 1993, and qualifies as prior art to the claims of the '593 patent under 35 U.S.C. § 102(b). DTX-733.

34. *Raffa II* describes that "[t]he (+)-enantiomer [of tramadol] had K_i values of only 1.33, 62.4 and 54.0 μM at *mu*, *delta* and *kappa* receptors, respectively. The (–)-enantiomer [of tramadol] had even lower affinity at the *mu* and *delta* sites (K_i=24.8, 213 and 53.5 μM, respectively. The (+)-enantiomer [of tramadol] was the most potent inhibitor of serotonin uptake (K_i = 0.53 μM) and the (–)-enantiomer [of tramadol] was the most potent inhibitor of norepinephrine uptake (K_i = 0.43 μM)." *Raffa II* at 1 (Abstract) and 4 (Table 1).

35. A POSITA would understand from *Raffa II* that (+)-tramadol has a better opioid/non-opioid mechanism of action profile than (-)-tramadol. 3.16.16 Martin Tr. 214:23-218:4; 221:18-20.

36. Sevcik, J., et al., "Effects of the central analgesic tramadol and its main metabolite, O-desmethyltramadol, on rat locus coeruleus neurones," *British J. Pharmacol.*, 110:169–176 (1993) ("*Sevcik*"), was published in September 1993, and qualifies as prior art to the claims of the '593 patent under 35 U.S.C. § 102(a). DTX-736.

37. *Sevcik* states that "[t]he results confirm that the analgesic action of tramadol involves both opioid and non-opioid components. It appears that (–)-tramadol inhibits the uptake of noradrenaline and via a subsequent increase in the concentration of endogenous noradrenaline indirectly stimulates α_2-adrenoceptors. (+)-O-desmethyltramadol seems to stimulate directly opioid μ-receptors. The effects of (+)-tramadol and (–)-O-desmethyltramadol consist of combined μ-opioid and α_2-adrenergic components." *Id.* at 1 (Abstract).

38. A POSITA would understand from *Sevcik* that (+)-tramadol and (-)-ODMT are individual compounds possessing both an opioid and non-opioid mechanism of action, and that among the two, (-)-ODMT is three-times more potent than (+)-tramadol. 3.16.16 Martin Tr. 218:9-220:5; 221:21-23; 222:7-21.

39. Based on the prior art as a whole that existed as of July 1994, a POSITA in selecting a lead compound for further development as an analgesic would consider tramadol and ODMT as lead compounds, and would have had an expectation that (+)-tramadol and (-)-ODMT would be more promising, with (-)-ODMT considered the most promising individual compound to select as a lead compound. 3.16.16 Martin Tr. 222:22-224:2.

40. In arriving at his conclusions about what the lead compound would be for a POSITA in July 1994, Professor Martin relied only on references which qualify as prior art to the claims of the '593 patent. 3.16.16 Martin Tr. 224:3-8.

41. Professor Martin did not consider the '593 patent or any Grünenthal documents in arriving at his conclusions with respect to the selection of a lead compound. 3.16.16 Martin Tr. 224:9-14.

42. Dr. Roush agreed that Professor Martin only relied on prior art references in arriving at his conclusion with respect to the selection of a lead compound. 3.22.16 Roush Tr. 72:22-73:9

43. Professor Martin did not use a hindsight driven analysis in reaching his opinions with respect to selecting a lead compound. 3.16.16 Martin Tr. 224:16-225:11.

3. The Prior Art Would Have Motivated a POSITA to Maintain the Known Pharmacophore of Tramadol and O-Desmethyltramadol

44. A POSITA would study the prior art and what the prior art says about SAR relationships for the lead compounds and identify the "pharmacophore" – the part of the lead compounds that is essential for biological activity. 3.16.16 Martin 226:25-227:16.

45. The most relevant prior art reference for the SAR of tramadol and related compounds is the 1978 *Flick* paper. 3.16.16 Martin Tr. 226:25-229:15.

46. Flick, K., et al., "Studies on chemical structure and analgesic activity of phenyl substituted aminomethylcyclohexanols," *Arzneimittel-Forschung*, 28:107-113 (1978) ("*Flick*"), was published in 1978, and qualifies as prior art to the claims of the '593 patent under 35 U.S.C. § 102(b). DTX-715 (German version); DTX-834 (also as Roush deposition exhibit 108; English version).

47. *Flick* states that "[t]he binding sites are an aromatic system, an intermediate chain and a basic center, so that the narcotic analgesics as their essential structural elements must have at least one aromatic ring, which is connected to a carbon chain via a bridging atom. The chain must carry a basic amino group at a distance of 2 to 3 C atoms." *Flick* at 112.

a. The Dimethylaminomethyl Group

48. It was known that the dimethylaminomethyl [$–CH_2–N(CH_3)_2$] moiety of tramadol significantly interacted with the opioid receptor, and a POSITA would not be motivated to make a change to this moiety of tramadol or *O*-desmethyltramadol. 3.16.16 Martin Tr. 330:4-240:8.

49. At Table 3, *Flick* shows that primary and secondary amine derivatives of tramadol are much less active (by at least factor of 10) in the analgesic assay employed and shows that replacement of methyl ($-CH_3$) groups with other alkyl and cycloalkyl (*e.g.* piperidinyl) groups results in significant loss of analgesic activity (by at least factor of 10). *Flick* notes that ". . .[i]n

the phenylcyclohexanols, the substitution possibility on the nitrogen is extremely limited" (*id.* at 113) and that "[t]he analgesic activity is associated with the dimethylamino group. The replacement of one or both methyl groups with hydrogen eliminates the activity. Substitution with higher alkyl groups or with substituents in which the nitrogen was integrated into a ring system also leads to loss of effect." DTX-834 at 112.

50. *Flick* shows that "[t]he analgesic activity is associated with the dimethylamino group. The replacement of one or both methyl groups with hydrogen eliminates the activity. Substitution with higher alkyl groups or with substituents in which the nitrogen was integrated into a ring system also leads to loss of effect." *Flick* at 112. Specifically, *Flick* shows that the amino analog (E450) and a methylamino analog (E419) are much less active than the dimethylamino analog (L201, tramadol). *Flick*, at Table 3. *Flick* also shows that the dimethylamino analog has a vastly superior analgesic effect compared to other dialkyl amino groups. *Id.* Hence, based upon the teachings of *Flick*, a POSITA would not want to change the dimethylamino group.

b. **Aromatic Oxygen Substituent**

51. *Flick* discloses that the analgesic effect of *O*-desmethyltramadol is about three-fold greater than tramadol. *Flick*, at Table 5; *compare* L235 (*O*-desmethyltramadol) *to* L201 (tramadol). Also at Table 5, *Flick* shows that derivatives having other substituents, including other O-alkyl derivatives, on the phenyl group have lesser analgesic effects. Therefore, a POSITA would be motivated to design analogs of tramadol that have a meta-hydroxy group. 3.16.16 Martin Tr. 247:2-252:13

52. *Flick* also states ". . . The free m-hydroxyl group gives the best strengthening of action . . ." *Id.*

53. At Table 5, *Flick* shows (1) that *meta*-OH substitution on the phenyl ring (L235) is optimal and about 3-fold more potent than tramadol (L201) with same toxicity – hence 3-fold better therapeutic index, (2) that replacing the O-methyl group on the phenyl ring with ethyl or benzyl does not increase the analgesic effect, and (3) that replacing O-methyl group on the phenyl ring with Cl, F or CF_3 leads to a loss of analgesic effect, and that *para*-O-methyl is not as potent as *m*-O-methyl. *Flick* further notes that "[t]he substitution of the phenyl radical with oxygen-containing functions strengthens the analgesic activity if the substituent is located in the meta-position." *Id.* at 112.

54. *Flick* discloses that for cyclohexanol analgesic agents "the free hydroxyl is the most advantageous of the oxygen-containing substituents on the bridge carbon, and esterification causes a practically complete loss of activity." *Id.* at 113.

c. **Bridge Carbon**

55. *Flick* states that "[t]he bridge carbon in 1-position on the cyclohexane ring can have a hydroxyl group as the fourth substituent, and with only slight loss of activity, a halogen atom. A hydrogen radical also leads to only a slight loss of activity in contrast to the general structural formula of the morphine analgesics" and that esterification of the hydroxyl group on the bridge carbon abolishes the analgesic activity almost completely (i.e., "Esterification of the hydroxyl group with acetic acid (L 205) or propionic acid (L 204) surprisingly leads to complete loss of analgesic activity.") (*Flick* at 111). *Flick* further states that "[i]n contrast to the standard piperidine derivatives, in the case of the cyclohexanes the bridge carbon may also be substituted with a hydrogen atom without this being associated with a substantial loss of activity." *Id.* at 113.

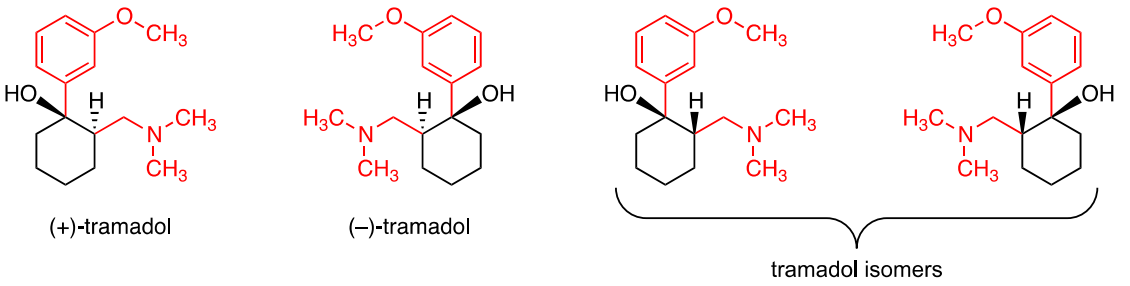
56. A POSITA would understand from *Flick* that the bridge carbon atome may be changed without significantly altering or losing biological activity. 3.16.16 Martin Tr. 241:16-245:10.

d. **Relative Stereochemistry**

57. The preferred stereochemistry for tramadol was already well established as of July 23, 1994. DTX-717 (German version); DTX-2052 (English version).

58. In terms of relative stereochemistry, a POSITA would have been motivated to design analgesics having the same stereochemical relationships at the stereogenic carbon atoms in the cyclohexane ring because this relationship between the phenyl ring and the dimethylamino side chain was known to be important for tramadol. 3.16.16 Martin Tr. 254:13-258:3.

59. *Frankus* states that "[t]he trans-isomer (of tramadol) was more active than the cis-isomer...." DTX-2052 at 1 (Abstract).



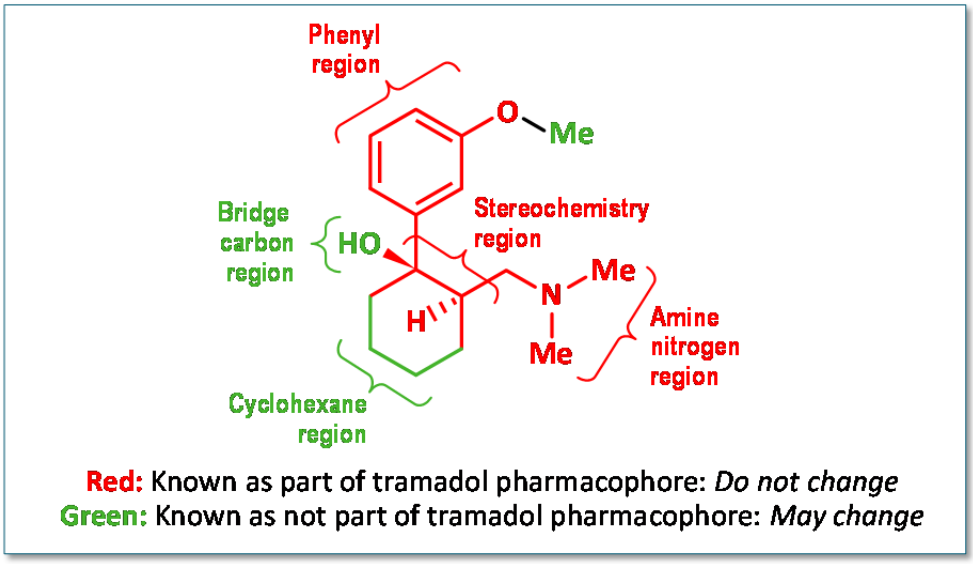
e. **Cyclohexane Ring**

60. *Flick* teaches that the design strategy used to design the phenyl-substituted aminomethyl cyclohexanols reported therein led to ". . . . compounds [that] can also be envisioned as highly simplified morphine derivatives, the structure of which was made very flexible by elimination of some parts of the ring." *Flick* at 112. A POSITA would have

recognized this strategy as a common and well-established approach to design analogs of morphine that would be expected to possess analgesic properties.

61. *Flick* also shows that 5- and 7-membered analogs of tramadol were less active and had a less favorable therapeutic index (*cf* E610, L201 and L257). *Id.* at Table 4. *Flick* states that "[t]he constriction or expansion of the cyclohexyl radical results in a loss of activity. This is much weaker in the case of ring expansion to cycloheptane than in the case of reduction to a cyclopentane ring." *Id.* at 112.

62. Based on the teachings form the prior art SAR studies on tramadol and related cyclohexanol analgesics a POSITA would identify the following as the pharmacophore for these lead compounds.

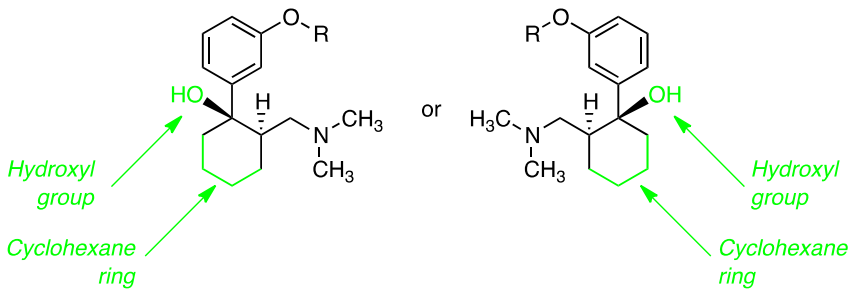


3.16.16 Martin Tr. 260:4-261:16.

4. **The Prior Art Would Have Motivated a POSITA to Replace the Bridge-Carbon Hydroxyl with a Hydrogen**

63. Given the known structural requirements and preferences for analgesic activity of tramadol and its active metabolite *O*-desmethyltramadol discussed above, a POSITA having experience with opioid analgesics in July 1994 would have considered two features as most

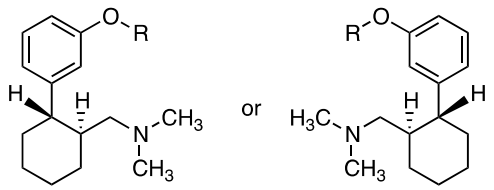
promising for possible modification that would reasonably lead to new compounds having similar or improved analgesic activity: these are the bridge-carbon hydroxyl group and the cyclohexane ring (shown in green below). 3.16.16 Martin Tr. 261:17-263:24.



a. **Bridge-Carbon Hydroxyl Group**

64. Among the handful of potential modifications of the bridge-carbon hydroxyl group of tramadol and *O*-desmethyltramadol is replacing it with a hydrogen atom or a chlorine atom. 3.16.16 Martin Tr. 262:7-17. It was known prior to July 1994 that these modifications had been performed for tramadol. *See, e.g.*, *Flick*, at Table 4. For example, *Flick* discloses that removing the bridge-carbon hydroxyl group surprisingly led to no significant loss of analgesic activity (*cf* L201, E386, and E609), although the therapeutic index in the tramadol series is slightly better (< 3-fold) for OH than Cl or H. *Id.* Esterification of the hydroxyl group led to significant loss of analgesic activity (*cf* L201, L205, and L204), so that would not be considered a promising option. *Id.*

65. A POSITA with experience with analgesics in July 1994 would have been motivated to replace the bridge-carbon hydroxyl group of tramadol or *O*-desmethyltramadol with a hydrogen atom and would have had a reasonable expectation that the resulting compounds shown below would possess pharmacological activity, including analgesic activity. 3.16.16 Martin Tr. 262:19-263:15.



R = CH_3 for enantiomers of tramadol
R = H for enantiomers of *O*-desmethyltramadol

66. A POSITA would be motivated to replace the bridge carbon -OH with a -H to simplify the molecule, in keeping with the opioid tradition of simplifying analgesics based on morphine. 3.16.16 Martin Tr. 262:19-263:2. The same change had already been made by *Flick* and the authors were surprised that the compound with the -H at the bridge carbon retained strong analgesic activity, and that would have been important to a POSITA. 3.16.16 Martin Tr. 263:3-15.

b. **Cyclohexane Ring - The Prior Art Would Have Motivated a POSITA to Prepare Open-Ring Compounds**

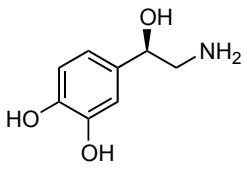
67. The prior art would have motivated a POSITA to modify the cyclohexane ring of tramadol and ODMT when designing analgesics with improved properties. 3.16.16 Martin Tr. 263:18-286:6;

68. One possible modification to the cyclohexane ring involves changing the ring size by either increasing or decreasing the number of methylene groups in the ring. See above ¶60. However, *Flick* discloses that the analgesic effects of 5- and 7-membered ring analogs of tramadol were about 3–15 fold less than for tramadol; the 5- and 7-membered ring analogs also have less favorable therapeutic indexes. *Id.* Hence, a POSITA would not would not have expected that expanding or contracting the cyclohexane ring would have led to an analgesic compound with similar or improved properties compared to tramadol. *Id.*

69. A POSITA would also not consider it promising to start adding substituents to the cyclohexane ring, an approach that would add complexity and be contrary to the traditional

approach of simplifying opioids in the morphine area (as discussed in the *Hennies* prior art reference). 3.16.16 Martin Tr. 266:18-267:10.

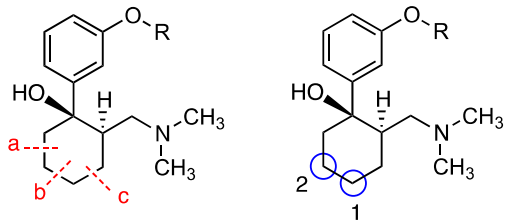
70. Another possible modification of the cyclohexane ring is inspired by the long tradition of simplifying morphine analogs by breaking bonds and removing rings, while retaining the morphine pharmacophore. Indeed, *Flick* notes that ". . . even extensively modified derivatives of morphine can have strong, typically morphine-like properties" and refers to ". . . synthesis of simple partial structures of morphine." *Flick* at 107. This structural simplification involves preparing a ring-opened compound to give acyclic (or "open chain") analogs of tramadol or O-desmethyltramadol that would be somewhat more flexible than tramadol. 3.16.16 Martin Tr. 267:11-269:15. The antinociceptive properties of tramadol were known to be mediated by μ-opioid and $\alpha_{\square}$-adrenergic (norepinepherine uptake inhibition) mechanisms. *See, e.g.*, *Sevcik* (DTX-736) *at Abstract*. Because norepinepherine (shown below) is an acyclic molecule that is more flexible than tramadol, a POSITA would have expected that making more flexible analogs of tramadol would be an attractive option, because such compounds might reasonably be expected to adopt conformations that would enable optimal interactions, and thus enhanced binding, at both $\alpha_{\square}$-adrenergic and μ-opioid receptors. 3.16.16 Martin Tr. 268:23-269:22.



Norepinepherine

71. Modification of the cyclohexane ring of tramadol or *O*-desmethyltramadol by preparing an "open chain" analog while maintaining the "stereochemistry region" of the tramadol pharmacophore could involve retaining all six carbon atoms of the cyclohexane ring, which

could be viewed as cleaving one of the carbon-carbon bonds labeled a-c in the ring (*Scission*). 3.17.16 Martin Tr. 18:13-22:21. Alternatively, modification of the cyclohexane ring of tramadol or *O*-desmethyltramadol while maintaining the "stereochemistry region" of the tramadol pharmacophore could involve eliminating one or two of the carbon atoms of the cyclohexane ring, which could be viewed as removing one or both of the -(CH_2)- groups in the ring encircled in blue as 1 or 2 (*Excision*). 3.16.16 Martin Tr. 270:24-271:2. These structural modifications are exemplified below for (+)-tramadol and (+)-*O*-desmethyltramadol:



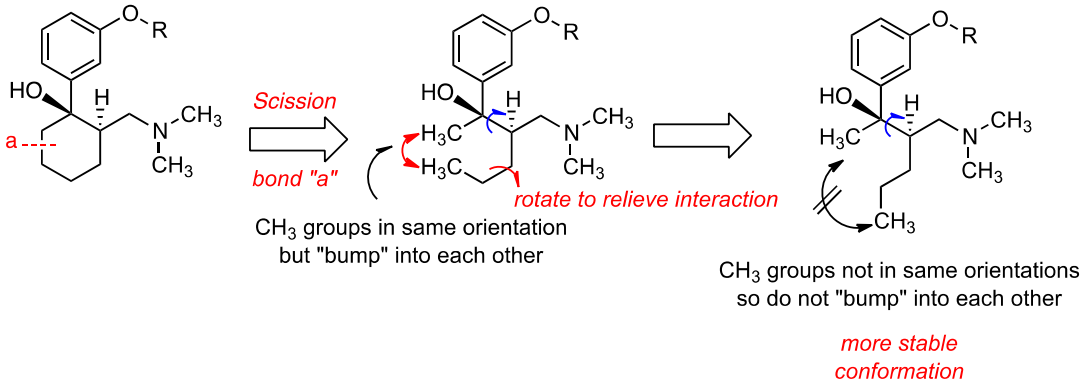
Scission *Excision*

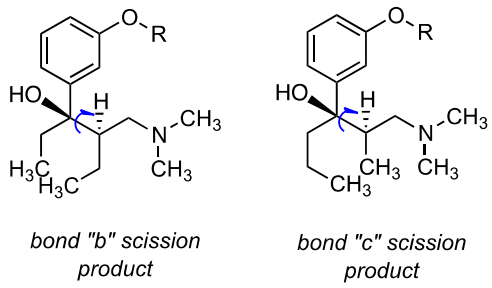
R = CH_3 for (+)-tramadol
R = H for (+)-*O*-desmethyltramadol

72. However, "scission" of a carbon-carbon bond in the cyclohexane ring of either tramadol or *O*-desmethyltramadol by cleaving bonds a, b, or c would not be expected by a POSITA as a promising option because the two methyl groups in the resulting "open chain" molecules could not occupy the same spatial positions as the corresponding methylene groups in the cyclohexane ring. 3.17.16 Martin Tr. 20:7-21:7; 21:11-22:21. If they did, they would "bump" into each other. *Id.* Hence, to avoid this close proximity, conformational changes will result as exemplified for cleavage of bond "a" of (+)-tramadol and (+)-*O*-desmethyltramadol in the figure below. *Id.* Scission of bonds labeled "b" and "c" leads to the related compounds shown below, and these may be analyzed similarly. *Id.*

73. A POSITA would expect an increase in conformational flexibility about the carbon-carbon bond between the stereogenic centers in the open chain molecules (see blue

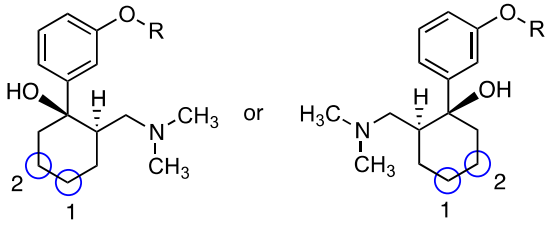
arrow) and understand from Spassov (DTX-739) at 3) that the two staggered conformations stabilized by an intramolecular hydrogen bonds would be preferred (as further discussed below).





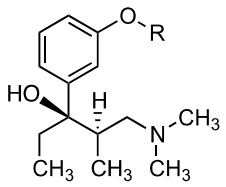
R = CH_3 for (+)-tramadol
R = H for (+)-*O*-desmethyltramadol

74. Preparing "open chain" analogs of tramadol or *O*-desmethyltramadol while maintaining the "stereochemistry region" of the tramadol pharmacophore may be viewed as eliminating one or both of the -(CH_2)- groups, which are encircled in blue below, from the cyclohexane ring. This structural modification may be viewed as "excision" and is depicted below for enantiomers of tramadol and *O*-desmethyltramadol. 3.17.16 Martin Tr. 23:1-25:19.



R = CH_3 for enantiomers of tramadol
R = H for enantiomers of *O*-desmethyltramadol

75. Among the two excision possibilities noted above by blue circles, making an "open chain" analog by eliminating the -(CH_2)- group encircled in blue and labeled as 1 above would provide "open chain" compounds of the general structure depicted below for (+)-tramadol and (+)-*O*-desmethyltramadol (*Id.*):

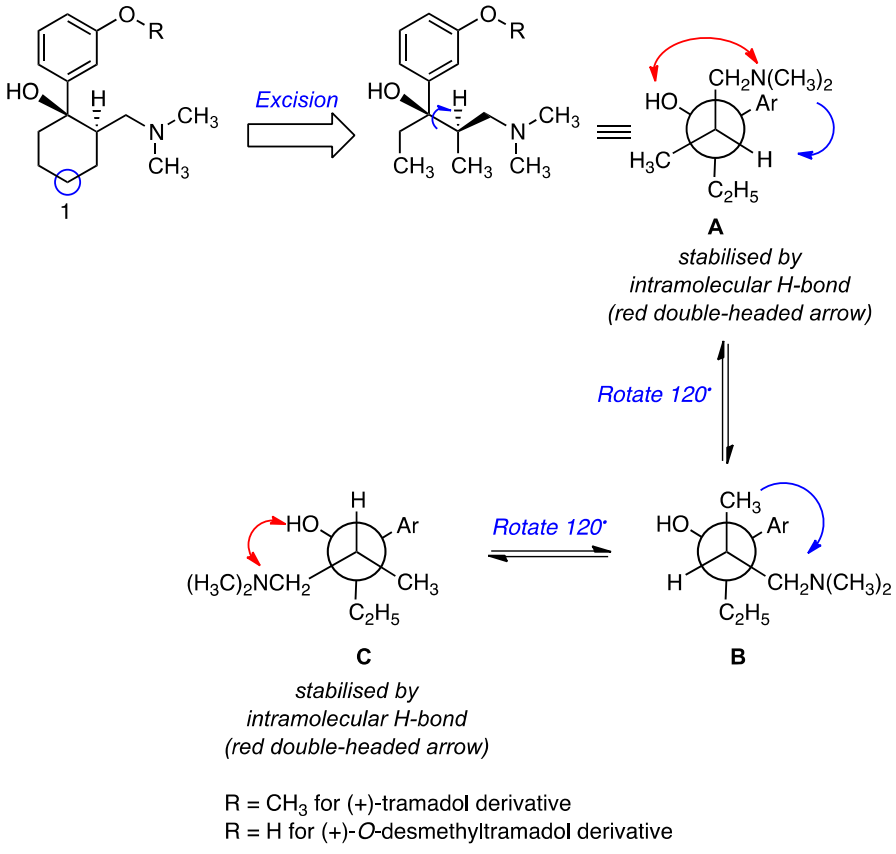


R = CH_3 for (+)-tramadol derivative
R = H for (+)-*O*-desmethyltramadol derivative

76. Compounds closely related to these "open chain" analogs of (+)-tramadol and (+)-*O*-desmethyltramadol were known in the prior art and reported in *Avramova* (DTX and *Spassov* (DTX-739). Thus, among the two choices of -(CH_2)- groups encircled above in blue, a POSITA would be guided by these prior art references to first eliminate the -(CH_2)- group labeled as 1. *Id.* Similar analogs may be envisioned for (–)-tramadol and (–)-*O*-desmethyltramadol.

77. It was also known prior to July 1994 that "open-chain" analogs of tramadol and *O*-desmethyltramadol closely related to the acyclic structures shown above possessed pharmacological activity, including analgesic, anesthetic, antidepressant, and antispasmodic activity. *See, e.g.*, *Avramova* and *Spassov* (DTX-739), discussed above. A POSITA with experience with opioid analgesics in July 1994 would thus have been motivated to first prepare the "open chain" analogs of tramadol or *O*-desmethyltramadol that arise conceptually by eliminating the -(CH_2)- group encircled in blue and labeled as 1 as described previously. In so doing, a POSITA would have had a reasonable expectation that the resulting compounds would possess pharmacological activity, including similar or improved analgesic activity, compared to tramadol and *O*-desmethyltramadol.

78. A POSITA would expect an increase in conformational flexibility about the carbon-carbon bond between the stereogenic centers in the "open chain" compounds (see blue arrow in second structure below). A POSITA would also understand from *Spassov* (DTX-739) at 3) that the two staggered conformations represented by the Newman projections **A** and **C** below may be stabilized by an intramolecular hydrogen bond. A POSITA would thus expect these two conformers to be of comparable stability and preferred over the conformation represented by the Newman projection **B** shown below. Of these two conformations, only conformer **A** allows the *m*-methoxy (or *m*-hydroxy) phenyl and the dimethylaminomethylene groups to preferentially adopt the same spatial orientations they do in (+)-tramadol or (-)-*O*-desmethyltramadol.



5. **Salt Selection**

79. The pharmaceutically acceptable salts of tramadol and *O*-desmethyltramadol, including the hydrochloride salts, were known in the art prior to July 1994 as the preferred forms. *See, e.g., Hennies* (DTX-691). Salt forms of active pharmaceutical ingredients were common as of July 23, 1994, and a POSITA would have been motivated to use a salt form of tapentadol in a pharmaceutical formulation. See, *e.g.*, Berge, S.M., *et al*., "Pharmaceutical Salts," *J. Pharm. Sci.*, 66(1):1-19 (1977) (DTX-176; "*Berge*") at p. 2 (providing a table of FDA-approved commercially marketed salts, which includes hydrochloride forms of many drugs). Because hydrochloride salts of APIs were common as of the early 1990's—indeed the hydrochloride was the most common salt (*see, e.g., Berge*, Table 1, p. 2)—a POSITA would have been motivated to use pharmaceutically acceptable salt forms of tapentadol, such as tapentadol hydrochloride, as required by the asserted claims of the '593 patent. 3.17.16 Martin Tr. 25:17-27:3.

6. **A POSITA Could Have Made Tapentadol Using Known Methods**

80. Given the prior art motivation to select and modify the lead compounds, tramadol and *O*-desmethyltramadol, and their individual stereoisomers, as discussed above, it would have been only a matter of routine experimentation for a POSITA to synthesize tapentadol and its pharmaceutically-acceptable salts, including tapentadol hydrochloride. 3.17.16 Martin Tr. 24;20-25:16. Dr. Roush provided no testimony to the contrary. *Id.*

1. The Composition and Methods Claims Would Have Been Obvious

81. Claims 8 and 117 of the '593 patent encompass "[a] method of treating a mammal suffering from pain" by administering an effective analgesic amount of tapentadol hydrochloride. DTX-1346 at 15-16 and 22.

82. As discussed above with respect to the asserted compound claims, by selecting and modifying the lead compounds from the prior art, a POSITA with experience in opioid analgesics would have had a reasonable expectation of success that the newly derived compounds, tapentadol and the "open chain" analog of (–)-*O*-desmethyltramadol, would have similar or improved analgesic properties. 3.17.16 Martin Tr. 27:4-21. The use to treat pain was obvious from the very pharmaceutical context in which a POSITA would have approached the project, and does not impart a valid patentable distinction to the "method of treating pain" recited in claims 8 and 117 of the '593 patent.

B. The Asserted Claims Lack Utility Under 35 U.S.C. § 101 and § 112/1

501. Dr. Wolf and Dr. Mogil each testified that their opinions and conclusions in connection with the '593 patent apply under either Defendants' or Plaintiffs' proposed definition of a POSA. (3/11/16 Mogil Tr. 260:5-21; 3/17/16 Wolf Tr. 57:24-58:15.)

502. Dr. Wolf and Dr. Mogil each testified that their opinions and conclusions in connection with the '593 patent were based on the Court's construction of "(–)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride(–21)," which appears in claims 61 and 117. (ECF No. 333 at 2; 3/11/16 Mogil Tr. 259:24-260:4; 3/17/16 Wolf Tr. 57:16-23.)

503. Dr. Wolf was admitted as an expert in organic chemistry, including stereochemistry and the synthesis, analysis, and characterization of optically active compounds." (3/17/16 Wolf Tr. 53:5-12.) Dr. Wolf's testimony was credible and convincing.

504. Dr. Mogil was admitted as an expert in animal modeling of pain, pain mechanism and assaying analgesic activity of compounds. (3/11/16 Mogil Tr. at 252:6-11.) Dr. Mogil's testimony was credible and convincing.

1. The Specification Contains No Testing About the "Desired Pharmacological Response"

505. A POSA would understand the following statement in the specification to be what the inventors intended to achieve and the asserted utility of the claimed compounds: "The underlying object of the present invention was to provide substances with an analgesic effect, which are suitable for the treatment of severe pain without giving rise to the side effects which are typical of opioids." (DTX 1346 at 1:59-2:5; 3/22/16 Roush Cross Tr. 104:13-106:3; 3/23/16 Ossipov Tr. 166:13-168:6.)

506. During prosecution of the '130 patent application, the Examiner understood the '593 patent's asserted utility to be analgesia without opioid side effects. (3/23/16 Ossipov Tr. 168:7-169:10; PTX 1600, Tab A at GRT-NUC00043829.)

507. As of 1994, a POSA understood that animal models to assess opioid side effects were known, and the '593 patent undisputedly contains no such testing. (3/23/16 Ossipov Tr. 169:11-170:4, 170:14-20, 172:6-8; 3/11/16 Mogil Tr. 257:10-20, 266:14-19; 3/22/16; 3/22/16 Roush Cross Tr. 104:13-106:3; 107:7-22.)

508. The specification also discloses that: "These substances are characterized by a pronounced analgesic effect which is significantly enhanced compared with that of tramadol," and contains no comparative (or other) testing with respect to tramadol. (DTX 1346 at 2:3-5; 3/23/16 Ossipov Tr. 171:23-172:3; 3/11/16 Mogil Tr. 261:18-262:9, 264:25-265:12; 3/22/16 Roush Cross Tr. 107:7-22.)

2. The Specification Does Not Establish Even Mere Analgesia

509. Claims 61 and 147 do not recite the term "analgesic" or "analgesia." (DTX 1346 at claims 61, 147.)

510. The specification contains no testing of any kind regarding the compound of

Example 25 (tapentadol), and a POSA would therefore not conclude that either the species recited in claims 61, 117, and 147 had efficacy as analgesics. (DTX 1346 at 22:15-40; 3/11/16 Mogil Tr. 262:10-264:15, 279:22-280:7; 3/17/16 Wolf Tr. 59:1-17, 66:2-17; 3/22/16 Roush Cross Tr. 107:23-108:19; 3/23/16 Ossipov Tr. 172:4-12.)

511. The specification presents no statistical analysis or confidence limit, and as of 1994 there were no accepted criteria as to what particular ED50 value would indicate that a compound was suitable to treat severe pain,with the result that a POSA could not draw conclusions about the data presented. (DTX 1346 at 21:54-22:40; 3/11/16 Mogil Tr. 279:22-280:7; 315:2-316:7; 3/23/16 Ossipov Tr. 162:4-13, 171:18-22, 172:24-25.)

512. A POSA understands that even the most structurally similar compounds (*i.e.*, enantiomers) can have profoundly different activity, and thus needs to assess whether a supposedly new compound had efficacy as an analgesic on a case-by-case basis, based on empirical data. (3/17/16 Wolf Tr. 55:16-56:11; 59:1-17; 3/17/16 Wolf Redirect Tr. 43:20-44:18; 3/11/16 Mogil Tr. 286:19-287:7, 291:4-11; 3/22/16 Roush Cross Tr. 115:15-116:17, 118:4-25; 3/23/16 Ossipov Tr. 171:23-172:3.)

513. A POSA would therefore not infer that the compounds of the asserted claims (including specifically the compound of Example 25) had efficacy as analgesics based on the limited presentation of data in the specification because the tested compounds were not known in the prior art, and some of the data are not even from single compounds but instead from mixtures of enantiomers. (DTX 1346 at 21:54-22:40; 3/22/16 Roush Tr. 121:6-122:9; 3/11/16 Mogil Tr. 262:10-264:15; 3/17/16 Wolf Tr. 59:1-60:3; 74:8-76:14.)

a. **The Writhing Test Is Not Reasonably Indicative of Analgesia**

514. As of 1994, numerous animal models of pain were known to a POSA, including the hot-plate, tail-flick, writhing, formalin, chronic construction injury, spinal nerve ligation,

complete Freund's adjuvant tests, as well as known tests of side effects and motor control. (3/11/16 Mogil Tr. 254:3-259:12.) A POSA understood the need to obtain data from at least more than one of these models in order to rule out known confounding effects and draw reasonable conclusions about the analgesic properties (if any) of a test compound. (3/11/16 Mogil Tr. 256:19-257:4.)

515. Because the sole pharmacological testing in the specification is the writhing test on mice, a POSA would find no convergent data from multiple animal models of pain known as of 1994. (DTX 1346 at 21:54-22-12; 3/23/16 Ossipov Tr. 172:6-8; 3/11/16 Mogil Tr. 257:10-20, 266:14-19.)

516. A POSA understood that the validity of any animal model of pain must be rooted in a scientific body of evidence. (3/23/16 Ossipov Tr. 190:25-191:15.)

517. Dr. Hammond's highly-respected chapter from 1989 surveyed and summarized the scientific literature about animal models of pain, and reflected a POSA's following understanding:

> "Arguments concerning the predictability of a specific model of nociception are counterproductive, as ***no model is reliably predictive***";
>
> "The inference of pain and its modulation in animals can be made ***only*** through the judicious use of ***complementary models*** of nociception ***and*** assessments of motoric function"; and
>
> "No conclusions should be based ***solely*** on alterations in reflex response in the absence of ***additional information*** on motor function and ***an additional*** behavioral measure of nociception."

(DTX 1576 at 77, 88; 3/11/16 Mogil Tr. 269:18-270:22.)[1]

518. A POSA would find no data from any complementary models of pain or tests of motor function in the specification, and would thus not conclude that the claimed compounds

[1] All emphasis added unless otherwise noted.

had efficacy as analgesics. (3/23/16 Ossipov Tr. 172:6-8; 3/11/16 Mogil Tr. 256:12-257:9, 262:10-20, 265:22-266:19.)

519. As of 1994, a POSA understood that, used alone, the mouse writhing test was not reasonably predictive of analgesia due to at least three fundamental limitations that necessitated obtaining convergent data from additional animal models. (3/11/16 Mogil Tr. 265:22-267:4, 285:19-286:2; 3/22/16 Ossipov Tr. 207:7-208:22 DTX 2057 at 321.)

520. Dr. Ossipov acknowledged a chapter from 1963 about the writhing test, which stated that: "However, the method is nonspecific and is not reliable for predicting the analgesic activity of new compounds, since many types of drugs are active in the test." (3/22/16 Ossipov Tr. 207:7-208:22 DTX 2057 at 321-322.)

521. ***Non-Specificity of the Writhing Test.*** First, a POSA understood that the writhing test was non-specific, meaning that compounds known not to be analgesic nonetheless produce a reduction in writhes as compared to controls. (3/11/16 Mogil Tr. 267:5-17.)

522. The non-specificity of the writhing test was documented as early as 1959 in the Hendershot & Forsaith paper that is also referenced in the specification. (3/11/16 Mogil Tr. 267:18-268:14; DTX 1346 at 21:52-67; DTX 170 at 239-240 & Table 3.)

523. The non-specificity of the writhing test was addressed in 1989 in Dr. Hammond's chapter, which stated that the "predictability of the writhing test has been ***impugned*** for this reason," and "[a]gain, this observation speaks to the importance of ***additional behavioral characterization of compounds***." (DTX 1576 at 88; 3/11/16 Mogil Tr. at 270:4-11.)

524. Even after 1994, Dr. Mogil and other pain scientists confirmed that non-specificity is a fundamental limit of the writhing test. (DTX 165 at 1031; DTX 177 at 68; 3/11/16 Mogil Tr. at 271:5-272:24, 272:25-273:10; Friederichs Depo. Tr. 173:22-174:18, 180:2-

13.)

525. ***Stress-Induced Analgesia and Sensitivity of the Writing Test.*** Second, it was known that a reduction in the observed number of writhes could easily be confounded by the phenomenon of stress-induced analgesia, whereby the reduced writhes were due to stress from handling of the animal, rather than any effect of the test compound. (3/11/16 Mogil Tr. 273:11-274:3; DTX 166 at p. 17-18; DTX 1576 at p. 79; DTX 177 at 66.)

526. As applied in the '593 patent, a POSA would recognize stress-induced analgesia would be a significant confound because the animals receiving the test compounds were restrained in order to force that compound down their throats via syringe, whereas the control animals had no corresponding restraint. (3/11/16 Mogil Tr. 275:7-276:22, 312:2-315:1.)

527. ***Motor Impairment and Sedation in the Writhing Test.*** Third, it was known that a mouse could exhibit decreased writhing due to motor impairment or sedation rather than a true analgesic effect of the test compound, and Dr. Hammond wrote that "No conclusions should be based … in the absence of additional information on motor function" and that "a decrease in the number of writhes is not indicative of antinociception if it accompanied by gross motoric disturbance…." (DTX 1576 at 77, 86.) The '593 patent contains none of the routine tests known as of 1994 to control for these confounding effects, such as the rotarod test (3/11/16 Mogil Tr. 276:23-277:15; 3/23/16 Ossipov Tr. 179:5-21, 181:2-19; Friderichs Depo. Tr. 224:16-24), which Dr. Ossipov, himself, has used as a control for motor function in connection with animal tests of analgesic activity. (3/23/16 Ossipov Tr. 179:5-21.)

528. On cross-examination, Dr. Ossipov acknowledged scientific literature documenting that a POSA understood the writhing test to be "not a valid animal model of" nociceptive pain, and does not evoke a consistent painful noxious stimulus, including in human

subjects. (3/23/16 Ossipov Tr. 197:22-200:5, 201:19-202:17; DTX 1576 at p. 75-77; 3/23/16 Ossipov Tr. 201:11-18; DTX 97 at 120-21.)

529. On cross-examination, Dr. Ossipov acknowledged scientific literature documenting that a POSA understood the writhing test "is ***nonspecific*** and is ***not reliable for predicting the analgesic activity of new compounds***, since many types of drugs are active in the test" (3/23/16 Ossipov Tr. 207:7-208:22; DTX 2057 at 321.)

530. Dr. Ossipov admitted that, in his 30 year career as the "animal models person," (3/23/11 Ossipov Tr. 112:14-16), none of his more than 100 publications on rodent models of pain has used the writhing test, (3/23/11 Ossipov Tr. 162:16-18, 163:4-8, 164:6-12, 165:5-25), and he has "never been motivated to defend" the writhing test during his career. (3/23/16 Ossipov Tr. 194:14-25.)

531. Dr. Ossipov admitted that, in his own scientific publications on rodent models of pain, he has relied on convergent data from multiple animal models of pain to reach conclusions about the analgesic activity of certain test compounds. (3/23/16 Ossipov Tr. 181:20-185:12; DTX 1669 at 227; 3/23/16 Ossipov Tr. 185:13-187:23, 189:15-18; DTX 1670 at 128; 3/23/16 Ossipov Tr. 189:19-191:15; DTX 1671; 3/23/16 Ossipov Tr. 202:3-25; DTX 1576 at 77; 3/23/16 Ossipov Tr. 192:3-196:2; DTX 1579.)

532. In connection with the standard he applied for utility, Dr. Ossipov admitted that, consistent with the body of scientific evidence before and after 1994, "no final conclusion should be based on a single test," and stated that by using the writhing test in the '593 patent, "we're not making a firm conclusion," and the intent is instead "the beginning of a study." (3/23/16 Ossipov Tr. 202:3-25; 204:1-9; 204:23-205:11; DTX 1576 at p. 88.)

3. Plaintiffs May Not Rely on Post-Filing Data to Support Utility

533. Based on the data presented in the specification, a POSA would have no basis to

conclude that the compounds of the asserted claims had efficacy as analgesics. (FOF505-531.)

4. **The Earliest Possible Priority Date is October 24, 2005**

534. The October 24, 2005 the Declaration Under 37 C.F.R. § 1.132 by Wolfgang Strassburger contained 100 pages of laboratory notebook entries containing data from multiple animal models of pain, such as the writhing test, hot plate test, and tail flick test. (3/11/16 Mogil Tr. 283:11-285:8; 3/23/16 Ossipov Tr. 175:21-177:6; DTX 1668.)

535. On their face, fifty of the laboratory notebook entries in the Strassburger Declaration bear dates after July 23, 1994, including three entries for the compound "BN200," which purportedly corresponds to the compound of Example 25. (3/23/16 Mogil Tr. 284:14-285:1; DTX 1668 at p. 59; 3/23/16 Ossipov Tr. 177:8-178:23.)

536. The data in the Strassburger Declaration represent the first instance when a POSA would have access to test results from ***multiple*** animal models about some of the claimed compounds, including "BN200." (3/11/16 Mogil Tr. 280:22-281:7; 3/23/16 Ossipov Tr. 178:2-23.)

537. The Strassburger Declaration was not submitted in response to an Office Action issued by the Examiner and was not otherwise requested by the USPTO Examiner. (3/23/16 Ossipov Tr. 174:18-175:11; 3/11/16 Mogil Tr. 285:9-18; DTX 946.)

538. Through the Strassburger Declaration, the Patentees attempted to rectify the absence of data from multiple animal models of pain in the specification. (3/11/16 Mogil Tr. 285:2-286:2; 3/23/16 Ossipov Tr. 175:12-176:20.)

539. The November 24, 1997 Declaration Under 37 C.F.R. § 1.132 of Helmut Buschmann lacks any indication that the subject data were available to a POSA as of July 23, 1994. (3/23/16 Ossipov Tr. 173:12-174:7; 3/11/16 Mogil Tr. 281:8-283:10.)

540. The Buschmann Declaration did not identify "Example 25" in its discussion, but

confusingly did identify "Example 25" in the data table. (3/11/16 Mogil Tr. 282:20-283:10; 3/17/16 Wolf Tr. 74:20-75:18.)

541. The Buschmann Declaration's data contained no statistics, which a POSA would require to assess whether the data presented have statistical significance. (3/11/16 Mogil Tr. 281:8-283:10.)

542. In the Buschmann Declaration, the data purporting to correspond to the compound of Example 25 showed less analgesic activity than other "threo" compounds, and no difference from the "erythro" compound. (3/11/16 Mogil Tr. 281:23-283:10.)

543. The Buschmann Declaration contains data only from the mouse writhing test. (3/11/16 Mogil Tr. 281:14-22.)

C. The Patent Was Clearly Obvious By October 2005

544. In 2002, the World Health Organization's Drug Information *International Nonproprietary Names for Pharmaceutical Substance (INN)* disclosed "tapentadol" to be an "analgesic," meaning a pain-relieving drug, along with tapentadol's chemical structure and formula. (3/17/16 Wolf Tr. 60:4-66:1; DTX 260 at 184; 3/22/16 Roush Cross Tr. 122:10-24:3.)

1. Claim 8

545. Of the over 11 million compounds in claim 8 (3/17/16 Wolf Tr. 81:16-82:5), the WHO reference disclosed only tapentadol. (3/17/16 Wolf Tr. 63:6-11.)

546. A POSA, based on the disclosure in the WHO reference of tapentadol as an "analgesic," would have been motivated to administer the tapentadol "analgesic" to treat a mammal, particularly a human, suffering from pain. (3/17/16 Wolf Tr. 62:1-8.)

547. A POSA would have had a reasonable expectation of success of administering in achieving a method of treating a mammal suffering from pain by administering the known "analgesic" tapentadol, because an "analgesic" is a substance that alleviates pain. (3/17/16 Wolf

Tr. 62:1-24; Friedrichs Depo. Tr. 165:15:21, 228:20-23.)

548. As of 2005, a POSA would have found the subject matter of claim 8 was obvious in light of the WHO reference, pharmaceutical references concerning pharmaceutical salts, and a POSA's background knowledge in the art. (3/17/16 Wolf Tr. 61:14-25; 3/22/16 Roush Cross Tr. 122:10-24:3.)

2. **Claims 61, 117, and 147**

549. As of 2005, a POSA would have known that pharmaceutical compounds, including the "analgesic" compound tapentadol, could successfully be formulated as pharmaceutically acceptable salts, including the hydrochloride salt. (DTX 176 at 2; DTX 1580 at 701-06; 3/17/16 Wolf Tr. 64:1-8; 65:4-14, 65:22-66:1.)

550. As to the hydrochloride salt in particular, a POSA understood that it was "by far" the most frequent choice among other known salts, and had a motivation to "immediately progress" to it, with a reasonable expectation of forming the hydrochloride salt, including of the known "analgesic" tapentadol. (DTX 1575 at 203; 3/17/16 Wolf Tr. 64:14-65:3, 65:22-66:1; *see also* DTX 1575 at 204; 3/17/16 Wolf Tr. 65:22-66:1.)

551. As of 2005, a POSA would have found the subject matter of claims 61, 117, and 147 was obvious in light of the WHO reference, pharmaceutical references concerning pharmaceutical salts, and a POSA's background knowledge in the art. (3/17/16 Wolf Tr. at 64:9-65:1; 3/22/16 Roush Cross Tr. 122:10-24:3.)

D. Claims 61, 117, and 147 Lack Written Description Under 35 U.S.C. § 112/1

1. **The Specification Fails to Convey Possession**

552. When named inventor Helmut Buschmann and his team at Grünenthal synthesized the compound "BN200," they initially did not know what compound they had made. (3/10/16 Buschmann Tr. 136:19-140:19; DTX 2000 at 76.)

553. Dr. Buschmann and his team at Grünenthal internally determined the structure of the "BN200" compound using some of the techniques that a POSA commonly would have used as of 1994 to prove the structure of a supposedly new compound. (3/10/16 Buschmann Tr. 123:3-10; 3/17/16 Wolf Tr. 53:15-54:14, 67:13-68:1, 68:2-71:4; DTX 222 at 8A; DTX 1581 at 2; DTX 274 at 1; DTX 264; 3/22/16 Roush Cross Tr. 124:25-126:21, 127:17-130:7.)

554. The '593 patent contains no structural data of any kind, including for the compound of Example 25. (3/17/16 Wolf Tr. 66:18-67:12; 3/22/16 Roush Cross Tr. 131:14-21, 141:15-25.)

555. In the '364 patent specification, the inventors acknowledged that: "***As proven by X-ray diffraction*** the 1R,2R configuration as shown in the drawing of example 25 is correct although the configuration is reported as (-)-(1R,2S)) . . . ." (DTX 304 at 1:49-54; 3/17/16 Wolf Tr. 77:16-79:20; Buschmann Tr. 157:8-15, 159:13-160:4.)

556. It was not until 2004 that the Patentees publicly "proved" to a POSA that the chemical structure depicted under Example 25 "is correct," based on XRPD testing. (DTX 304 at 1:49-54; 3/17/16 Wolf Tr. 53:15-54:14, 67:13-68:1, 68:2-71:4, 77:16-79:20; 3/9/16 Buschmann Tr. 157:8-15, 159:13-160:4; 3/22/16 Roush Cross Tr. 141:3-14; PTX 871 at 3253)

557. As of 1994, consistent with fundamentally basic practice in organic chemistry, to understand what the inventors possessed, a POSA would require structural data generated from commonly used techniques, including the XRPD technique capable of identifying specific stereochemistry. (3/17/16 Wolf Tr. 53:15-54:14, 66:18-71:4; DTX 222 at 8A; DTX 1581 at 2; DTX 274 at 1; DTX 263 at Exs. 5-8, 10, 15, 17-19, 21; DTX 264 at Exs. 2-3, 5-8, 10, 15, 17-19, 21.)

558. The '593 patent discloses only a melting point range and a specific optical

rotation for the compounds of Example 24 and 25, which indicate nothing about chemical structure, indicate that those compounds are not enantiomers, and does not even correspond to the melting point of tapentadol hydrochloride. (3/17/16 Wolf Tr. 56:12-24, 66:18-67:12, 71:15-72:19; DTX 1346 at Exs. 24-25; 3/10/16 Buschmann Tr. 126:24-128:7; DTX 1414 at 6.)

559. The Court's claim construction of the "(–21)" terms requires "the compound" that is depicted in the formula under Example 25, and a POSA would never exclude any empirical data provided in the specification about a supposedly new compound. (3/17/16 Wolf Tr. 72:20-73:20, 3/17/16 Wolf Redirect Tr. 42:20-43:16; 3/22/16 Roush Cross Tr. 133:21-134:22.)

560. A POSA understands that multiple variables can cause even known chemical reactions to yield products other than expected. (3/10/16 Buschmann Tr. 121:1-4, 121:11-22; 3/17/16 Wolf Cross Tr. 12:20-13:5, 13:19-14:21.)

2. **The Prosecution History Fails to Convey Possession**

561. The prosecution history does not convey to a POSA that the inventors believed they possessed the claimed (1R, 2R) species. (3/17/16 Wolf Tr. 73:21-74:7.)

562. In stereochemistry, "R" and "S" descriptors convey fundamental information about the spatial arrangement of the compound, which undisputedly has important implications for its activity. (3/17/16 Wolf Tr. 55:2-56:11; DTX 1574; 3/10/16 Buschmann Tr. 119:18-120:21).

563. The original '737 patent application disclosed Example 25 as (1**S**, 2**S**), which is not the claimed (1**R**, 2**R**) species, yet the inventors signed a sworn declaration that the specification was true and correct. (DTX 950 at 30; 3/17/16 Wolf Tr. 74:8-75:5 3/10/16 Buschmann Tr. 130:14-131:16, 133:7-16, 133:23-134:5; DTX 1350 at 1.)

564. In November 1997, the inventors purported to "correct inadvertent inconsistencies" in Examples 24 and 25 by amending (1**S**, 2S) to (1**R**, 2S), which is not the

claimed (1**R**, 2**R**) species, and stated that "[s]upport for the amendments is found in the ***original formulas*** in Examples 24 and 25." (DTX 950 at 30; 3/17/16 Wolf Tr. 75:6-76:6; 3/10/16 Buschmann Tr. 145:19-146:24.)

565. The original '737 patent specification issued with the (1R, 2S) description of Example 25, not the claimed (1R, 2R) species. (DTX 668 at 20:1-24; 3/17/16 Wolf Tr. 76:7-14.)

566. It was not until July 2003 that the the inventors amended Example 25 from (1R, 2**S**) to the claimed (1R, 2**R**) species. (DTX 944 at 14; 3/17/16 Wolf Tr. 76:15-77:6.)

E. Claims 61, 117, and 147 Fail the Original Patent Rule Under 35 U.S.C. § 251(a)

567. The specification of the original '737 patent does not disclose the (1R, 2R) tapentadol species that is the subject of reissue claims 61, 117, and 147. (3/22/16 Bernstein Tr. 18:14/16; 3/17/16 Wolf Tr. at 80:9-18.) Instead, in the '737 patent, Example 24 discloses a (1S, 2R) compound and Example 25 discloses a (1R, 2S). (PTX 668, at 18:21-20:24; 3/17/16 Wolf Tr. at 80:9-18.)

568. The named inventor Dr. Buschmann agreed "that there was a contradiction between the structure and the stereochemistry that's designated" in Example 25 of the '737 patent. (3/10/16 Buschmann Tr. at 157:8-158:7; *see also* 3/17/16 Wolf Tr. at 78:9-79:20.) Dr. Wolf provided unrebutted testimony that in light of the contradiction, the (1R, 2R) species was not clearly and unequivocally disclosed in the original '737 patent specification. (3/17/16 Wolf Tr. at 80:9-18; 3/22/16 Buschmann Tr. at 18:14-21; 3/22/16 Berstein Tr. 19:2-6.) Grünenthal also touted the absence of disclosure of tapentadol in the '737 patent in responding to the Examiner's rejection of the '130 patent application. (PTX1600 (Tab F) at GRT-NUC00043980–81; PTX1600 (Tab G) at GRT-NUC00044066–67.)

569. Thus, species claims 61, 117, and 147 fail the original patent rule because the

'737 parent specification does not clearly and unequivocally disclose the newly claimed invention as a separate invention.

F. Claim 8 Is Not Enabled Under 35 U.S.C. § 112/1

570. The quantity of experimentation necessary to make and use the full scope of claim 8 would be excessive and undue. (3/11/16 Mogil Tr. at 288:21-289:4; Wolf Tr. at 80:19-86:6.)

571. ***Breadth of Claims.*** There is no dispute that claim 8 encompasses over 11 million compounds and over 600 million "salts thereof with a physiologically acceptable acid." (3/17/16 Wolf Tr. 81:16-82:7, 81:16-82:7; 3/11/16 Mogil Tr. at 286:19-287:4; 3/23/16 Ossipov Tr. 209:4-11.)

572. ***Quantity of Experimentation.*** In order to make and use the full scope of claim 8, a POSA would need to first synthesize, purify, and identify each of the compounds, and then perform appropriate animal model testing on a compound-by-compound basis to assess purported analgesic activity. (3/11/16 Mogil Tr. at 286:19-287:7; Roush Tr. at 125:24-126:7.) This process would require 10-12 days per compound (3/11/16 Mogil Tr. at 287:8-17; Wolf Tr. at 80:19-86:6), and even for just 1,000 compounds, the process would require years to perform. (3/23/16 Ossipov Tr. at 209:12-212:7.)

573. Grünenthal's internal "Tramadol Analog Project" documents from the mid-1990s demonstrates its own recognition of the need to test for analgesic properties on a compound-by-compound basis. (DTX 1144 at p. 45; 3/11/16 Mogil Tr. at 289:8-18.)

574. ***Amount of Direction or Guidance Presented in the Specification.*** The specification's sole direction on how to determine whether one of the myriad supposedly new compounds in claim 8 has analgesic activity is to perform the writhing assay on mice, which a POSA would understand to be insufficient standing alone. (3/11/16 Mogil Tr. at 290:10-18.)

575. ***Presence or Absence of Working Examples.*** The specification discloses only a

small number of examples and test compounds provided in the TABLE of the specification. (3/11/16 Mogil Tr. at 290:19-291:3; DTX 1346 at 22:15-40.)

576. ***Unpredictability of the Relevant Art.*** Dr. Mogil testified that analgesic activity of supposedly new compounds must be determined empirically for each compound. (3/11/16 Mogil Tr. 291:4-11; Friedrichs Depo. Tr. 214:17-22.) Dr. Roush and Dr. Ossipov conceded that in the field, activity of ostensibly novel compounds is determined empirically. (3/22/16 Roush Tr. 124:4-128:5; Ossipov Tr. 210:4-10.)

577. ***State of the Prior Art.*** As of July 1994 (and October 2005), it is unrebutted that a POSA would know that using only the writhing test was insufficient to establish any analgesic effect. (3/11/16 Mogil Tr. 291:12-18.)

578. ***POSA's Skill Level.*** A POSA's high level of skill would lead him or her to demand: valid assays, sound methodology, and statistical scrutiny. (3/11/16 Mogil Tr. 291:19-292:1.)

II. THE CLAIMS OF THE '364 PATENT ARE ANTICIPATED BY THE '737 PATENT

A. The '364 patent is anticipated

1001. Dr. Jonathan Steed is a Professor of Chemistry at Durham University in Durham, England. He is an expert in chemistry and crystallography. 3/15/16 Steed Tr. 10:7-13.

1002. The earliest filing date of the '364 patent is June 28, 2004. DTX 304; 3.15.16 Steed Tr. 75:24-25. Asserted claims 1-3 of the '364 patent cover Form A of tapentadol hydrochloride, or mixtures of Forms A and Form B. DTX 304; 3/15/16 Steed Tr. 10:14-19. Asserted claim 25 is directed to a solid dosage form containing Form A. DTX 304.

1003. There are only two polymorphs of tapentadol hydrochloride, Forms A and B. 3/15/16 Steed Tr. 11:18-23.

1004. A compound displays polymorphism when there are two ways of packing a particular molecule within three dimensional space, resulting in two different crystal structures. 3/15/16 Steed Tr. 12:4-17. Each polymorph will have a unique X-ray powder diffraction ("XRPD")—a "fingerprint"—used to distinguish one polymorph from another. 3/15/16 Steed Tr.13:15-22.

1005. CG 5503 and BN 200 both refer to tapentadol. 5/1/15, Dep. Tr. Lischke, 27:1-4; 3/26/15, Dep. Tr. Fischer, 125:11-15; 3/10/16 Buschmann Tr. 202:3-4.

B. Example 25 of the '737 patent results in Form A

1006. U.S. Patent No. 6,248,737 ("the '737 patent") issued on June 19, 2001, more than one year before the filing of the earliest application to which the claims of the '364 patent may claim priority and is prior art under 35 U.S.C. §§ 102 (a) or (b).

1007. The statement of allowability issued by the USPTO for the '364 patent identifies the closest prior art as the '737 patent. DTX 1361 at 6; 3/16/16FF Matzger Tr. 84:2-14.

1. University of Wisconsin ("UW") reproduction

a. **Step 3 of Example 25 creates the tapentadol molecule and its crystal form.**

1008. Example 25 of the '737 patent discloses the synthesis of tapentadol hydrochloride. DTX 752 at 22:1-25; 3/10/16 Buschmann Tr. 174:21-25; DTX 920 at 19:13-30; 3/15/16/ Steed Tr. 14:11-22. Example 25 incorporates three synthetic steps that are listed in Example 24. 3/15/16 Steed Tr. 14:6-10. Example 24 and 25 are only different in that their starting materials are opposite enantiomers— molecules with "opposite handedness." 3/15/16 Steed Tr. 14:6-10; 3/10/16 Buschmann Tr. 175:1-15, 178:16-24; DTX 920 at 18:61-63, 19:24-25. The products of steps 1 and 2 in Example 25 are purified as part of those steps and, as a result, each intermediate compound should be chemically pure. 3/10/16 Buschmann Tr. 211:16-18; 3/15/16 Steed Tr. 15:6-10.

1009. Tapentadol is not formed until the third step of Example 25 and is labeled as (-21). 3/15/16 Steed Tr. 14:1-6-10, 18-22; DTX 752 at 20:15-16. That third step starts with a compound identified as (-23)[2] which is different from tapentadol because it has a methoxy ("OMe") on the ring structure. 3/15/16 Steed Tr. 16:22-17:2; 3/10/16 Buschmann Tr. 175:21-176:1; DTX 920 at 18:61-19:11. The chemical reactions in Step 3 remove the methyl ("Me") group and convert the methoxy to a hydroxyl group ("OH"). 3/15/16 Steed Tr. 16:22-17:2. The (-23) precursor is a solid and is dissolved in concentrated hydrobromic ("HBr ") acid at which point it is no longer a crystalline solid, it is in solution. 3/10/16 Buschmann Tr. 176:8-21; DTX 920 at 18:64-65.

1010. The Step 3 reactions first result in the free base form of tapentadol—tapentadol without the hydrochloride—in solution so it does not have a crystal structure. 3/15/16 Steed

[2] The compound labeled as (-23) in Example 25 is also labeled as Bu 351 internally at Grünenthal. (3/10/16 Buschmann Tr. 183:21-24).

Tr.16:22-17:2; 17:12-18. TMCS/water is then added which allows hydrochloric acid to form and causes the final product, tapentadol hydrochloride, to crystallize out of solution. 3/15/16 Steed Tr. 14:15-22, 17:6-11; 3/21/16 Bernstein Tr. 262:17-23. "So that very last step is the only one that's relevant in terms of defining the polymorphic form and of course the conditions under which it occurs." 3/15/16 Steed Tr. 17:19-21.

b. **UW faithfully followed Example 25 and got Form A**

1011. Scientists at the University of Wisconsin ("UW") reproduced Example 25, starting at Step 3 of the process, which is the appropriate starting point. 3/15/16 Steed Tr. 28:25-29:4. As Dr. Steed explained, "[i]t's the one [step] that actually makes the Tapentadol molecule and then subsequently crystallizes it as Tapentadol []. So that's absolutely the place to begin if you are interested in the crystal form of Tapentadol hydrochloride." 3/15/16 Steed Tr. 29:5-12.

1012. The UW scientists faithfully reproduced Example 25 of the '737 patent. They obtained the starting material for Step 3—compound (-23)—from a company called Norac Pharma. 3/15/16 Steed Tr. 37:13-15; DTX 298 at 2. The UW scientists analyzed the starting material (-23) to ensure that it was the proper starting material using H-NMR, C-NMR, melting point, and optical rotation techniques. DTX 299 at 2; 3/15/16 Steed Tr. 20:2-21:1. The results of all these tests were consistent with data reported for (-23). DTX 299 at 2; 3/15/16 Steed Tr. 28:20-24. In addition, the starting material was accompanied by a certificate of analysis (DTX 299 at 8) that reported the result of numerous tests conducted on the material to confirm it was not contaminated with impurities, including inorganic impurities that would not be detected by NMR techniques. 3/15/16 Steed Tr. 24:9-28:19.

1013. Prof. Steed explained that chemists "like to start with pure starting material so the impurities don't interfere with the final product." 3/15/16 Steed Tr. 22:19-22. UW ran tests on the starting material to "check for the identity of the molecule and a check for whether there's

any impurities observed." 3/15/16 Steed Tr. 22:15-18. The testing done by UW along with the certificate of analysis assures the starting material was the right molecule, and it was pure. 3/15/16 Steed Tr. 28:20-24. Dr. Roush did not dispute that UW purchased appropriate starting material and correctly performed what he called "Step 4." 3/22/16 PM Roush Tr. 42:25-43:6.

1014. Dr. Bernstein did not question the appropriateness of the starting material that the UW used. 3/21/16 Bernstein Tr. 264:18-265:2. His only criticism was that UW reproduction "didn't go at that time to the beginning of the patent." 3/21/16 Bernstein Tr.265:2-3. He offers no explanation for why or how that matters to the polymorph issue in this case. Dr. Bernstein testified it does not matter what form one starts with when doing a crystallization if the starting material is going to be dissolved. 3/21/16 Bernstein Tr. 293:22-24.

1015. Dr. Bernstein did not analyze the three steps of the Example 25 synthetic process. 3/21/16 Bernstein Tr. 261:23-262:6. He had not "looked at all those steps in any detail." 3/21/16 Bernstein Tr. 262:3-6. Dr. Bernstein's understanding of the synthetic steps that Marita Mueller carried out in her attempted reproduction of Example 25 is based entirely on Dr. Roush's report and opinion. 3/21/16 Bernstein Tr. 265:4-17.

1016. Dr. Roush's only criticism of the UW reproduction is that UW did not personally perform all the steps listed in Example 25. 3/22/16 PM Roush Tr. 42:22-43:6. Dr. Roush offered no theories or explanations as to whether any step in the process occurring before what the patent calls Step 3 could affect the polymorphic form of the final product. 3/22/16 PM Roush Tr. 150:18-23. In fact, Dr. Roush testified that he had "not considered any of the issues concerning polymorphs in this case." 3/22/16 PM Roush Tr. 145:17-22.

1017. Dr. Buschmann admitted that using the right starting material for step 3 in Example 25 is all that matter to get the right crystals:

Q: Your testimony is as long as you have the right starting material, that plus 23 or minus 23 in the case of tapentadol, Example 25, that's all that matter to get the right crystal, correct?
A: If you use the procedure to crystallize it how it is written –
Q: And when you say the procedure, how it is written, you are referring to the third step portion of the procedure, correct?
A: Correct.
Q: And when you follow that procedure, my question is is it possible that because of the differences in the ingredients used, the person following the patent specification could get a different result in polymorphic form that the person following the lab notebook? Is it possible?
A: No, in my mind it wouldn't be possible.
Q: Wouldn't be?
A: Possible. Because you are following the same exact procedure with the same qualifications and the same information as the compounds. And if you follow this procedures even just to exchange a different step, it shouldn't result in a different product.
3/10/16 Buschmann Tr. 192:8-193:5.

1018. Additionally, Dr. Roush states that the result of performing the reactions in a different order is "very, very similar" to the result of performing the reaction steps as set forth in Example 25. 03/22/2016 PM Roush Tr. 24:16-22.

1019. The UW scientists recorded their reproduction of Example 25 in a laboratory notebook. DTX 298. Dr. Steed reviewed this notebook and concluded that the UW reproduction was a faithful reproduction of Example 25. The UW scientists faithfully followed each operation described in Example 25, listed below:

1. 4.3 g of (-23) added to 100 ml of HBr (hydrobromic acid). 3/15/16 Steed Tr. 30:8-31:8; DTX 298 at 3.
2. The mixture was then heated under reflux for two hours. 3/15/16 Steed Tr. 31:9-18; DTX 298 at 3.
3. After cooling to room temperature, the reaction mixture was concentrated under the vacuum from a water pump. 3/15/16 Steed Tr. 31:19-32:6; DTX 298 at 3.
4. The residue was treated with concentrated sodium hydrogen carbonate solution until an alkaline reaction was obtained. 3/15/16 Steed Tr. 32:7-23; DTX 298 at 3.
5. After extracting twice with 50 ml of dichloromethane. 3/15/16 Steed Tr. 32:24-33:8; DTX 298 at 3.

6. The combined organic phases were dried over sodium sulphate. 3/15/16 Steed Tr. 33:10-18; DTX 298 at 3.
7. Dichloromethane was then distilled off under vacuum. 3/15/16 Steed Tr. 33:19-34:6; DTX 298 at 3.
8. The residue was taken up in 2-butanone. 3/15/16 Steed Tr. 34:7-16; DTX 298 at 3.
9. After addition of trimethylchlorosilane ("TMCS")/water mixture, tapentadol HCL (-21) crystallized out. 3/15/16 Steed Tr. 34:17-35:24; DTX 298 at 3.

1020. The UW scientists premixed trimethylchlorosilane ("TMCS") and water before adding it to the reaction solution, just as required by Example 25. DTX 298 at 3; 3/15/16 Steed Tr. 34:22-25. Dr. Steed explained that it is the reaction between TMCS and water that generates hydrochloric acid that is then reacted with tapentadol in solution. The TMCS, if added directly to the reaction solution containing tapentadol, would react with molecules other than water, resulting in unwanted side reactions. 3/15/16 Steed Tr. 35:5-11.

1021. As Example 25 teaches, the UW scientists obtained white solid crystals from solution upon addition of the TMCS/water mixture to the solution containing tapentadol. DTX 298 at 3; 3/15/16 Steed Tr. 35:15-22. Dr. Steed concluded that the UW scientists faithfully replicated the procedure as described in Example 25. 3/15/16 Steed Tr. 35:25-36:10.

1022. The final product of the UW reproduction was a white solid. DTX 298 at 3; 3/15/16 Steed Tr. 36:11-14. The UW scientists characterized their final product using H-NMR, C-NMR, melting point and optical rotation. DTX 298 at 3-4. All these tests indicated that the product was tapentadol hydrochloride. 3/15/16 Steed Tr. 36:15-21; 38:13-23. Dr. Roush and Dr. Bernstein do not dispute that the UW reproduction resulted in tapentadol hydrochloride.

1023. The UW scientists also used XRPD to identify the polymorph of tapentadol hydrochloride they had made. DTX 297. The XRPD pattern indicated that the UW reproduction resulted in a mixture of Forms A and B of tapentadol hydrochloride. DTX 297 at 3; 3/15/16 Steed Tr. 39:3-15. Dr. Steed compared the XRPD pattern for the UW product with Figure 1 in

the '364 patent—a Form A pattern—to show that it was also "essentially the same" as the Form A pattern in the UW result. 3/15/16 Steed Tr. 40:25-41:2. Plaintiffs' polymorph expert, Dr. Bernstein, agreed that the XRPD pattern for the UW product contained Form A. 3/22/16 Bernstein Tr. 6:8-11.

2. **Plaintiffs admit that Example 25 results in Form A**

1024. Example 2, 3, 5, 9, and 11 of the '364 patent begins with Tapentadol that is prepared in accordance with Example 25 of European Patent 693,475. 3/11/16 Gruss Tr. 55:11-14; 3/16/16FF Matzger Tr. 93:8-18; DTX 304. Example 25 of the European Patent is the same as Example 25 in the '737 patent. 3/11/16 Gruss Tr. 55:15-18; 3/16/16FF Matzger Tr. 89:1-4; DTX 154. The starting material that was used for Example 2 was not Form B tapentadol, as stated in the patent (DTX 304 3:1-15), but rather Form A. 3/16/16FF Matzger Tr. 93:19-94:22; DTX 1001 at 5, 13.

1025. During Discovery, Defendants asked Plaintiffs to "[i]dentify by Bates-numbers all documents reflecting the design, execution, results and analyses for each of Examples 1-16 in the '364 Patent." DTX 144 at 7. In response, Plaintiffs stated "[d]ocuments that support Examples 2 and 3 of the '364 Patent can be found at GRT-NUC00021090-21277 including 21094, 21103, 21136." DTX 144 at 9.

1026. Plaintiffs' response referred to SSCI's Final Report. (DTX 1001). SSCI's Final Report "describes an investigation of the solid forms of CG 5503 (also known as BN 200)." 3/11/16 Gruss Tr. 60:21-25; DTX 1001 at 1. It confirms that the material used for the tests in the report was Form A Tapentadol. 3/11/16 Gruss Tr. 16:17-23; 5/1/15 Dep. Tr. Lischke 50:18-52:7, 57:14-58:9, 58:19-59:3, 59:6-7, 59:9-10, 59:12-18; 3/26/15 Dep. Tr. Fischer 102:5-10, 107:12-16; DTX 1001 at 5, 13. The page at production number GRT-NUC00021094 states that "[t]he CG5503 sample received from Grünenthal is summarized in Table 1." 3/11/16 Gruss Tr. 61:1-9;

DTX 1001 at 5. In turn, Table 1 identifies the CG5503 Tapentadol sample received from Grünenthal as Form A. 03/11/16 Gruss Tr. 61:24-62:2; DTX 1001 at 13.

1027. There is no reason to dispute Grünenthal's interrogatory response confirming that Example 2 of the '364 patent comes from the SSCI Final Report. 3/11/16 Gruss Tr. 56:25-57:6. And in any event, "there was only one sample lot [of tapentadol] that was received by SSCI" from Grünenthal. 3/11/16 Gruss Tr. 62:10-13. Dr. Fischer testified that Grünenthal only ever sent samples of Form A to SSCI. 3/26/15 Dep. Tr. Fischer 102:5-10, 107:12-15.

1028. The SSCI Final Report identifies the different routine solvents and conditions that SSCI used in a polymorph screen. 3/11/16 Gruss Tr. 62:19-63:4, 63:13-64:2; DTX 1001 at 14-15, Table 3. The Final Report provides XRPD diffraction for a sample labeled "631-03-02." DTX 1001 at 47; 3/11/16 Gruss Tr. 65:1-8. Per table 3 of the Final Report, sample 631-03-02 was screened for polymorphs using acetone as a solvent and was subject to "SE," which stands for slow evaporation. 3/11/16 Gruss Tr. 65:16-22, 66:7-15; DTX 1001 at 14-15. Dr. Gruss admitted that those are the same conditions used in Example 2 of the '364 patent. 3/11/16 Gruss Tr. 66:16-24; DTX 304. According to Table 3 of the Final Report sample 631-03-02 resulted in Form A tapentadol. 3/11/16 Gruss Tr. 65:9-22; DTX 1001 at 14.

1029. Therefore, according to Plaintiffs' own admissions, following Example 25 of the '737 patent results in Form A tapentadol, not Form B.

B. Plaintiffs never tested Example 25 as written

1. Buschmann batch #00 did not follow example 25 and no data for batch #01

1030. Dr. Buschmann first synthesized tapentadol hydrochloride, referred to as batch #00, on January 26, 1994. 3/10/16 Buschmann Tr. 26:10-27:5, 28:13-19; PTX 345. The second batch, batch #01 was synthesized in April 1994. 3/10/16 Buschmann Tr. 37:11-38:1; DTX 1138.

1031. Dr. Buschmann's batch #00 was made using a process that is different from Example 25. Prof. Steed reviewed Dr. Buschmann's lab notebook documenting the batch #00 synthesis. DTX 974; 3/15/16 Steed Tr. 54:7-16. Dr. Buschmann never carried out step 3 of Example 25. He used a completely different starting material for the last step of the synthesis. It was a molecule that already had an OH group on the ring—rather than the methoxy group (MeO) in (-23)—but had a chloro (Cl) group that was removed in the last step to get tapentadol free base that was then crystallized as the hydrochloride salt. DTX 974; 3/15/16 Steed Tr. 54:17-55:7. Dr. Buschmann agreed that he used a different starting material. 3/10/16 Buschmann Tr. 183:21-184:4. Dr. Buschmann also agreed that the method he used to synthesize batch #00 does not match the protocol in Example 25 of the '737 patent "because the sequence was different from batch 0." 3/10/16 Buschmann Tr. 182:17-20. Dr. Roush himself does not view Batch #00 as a faithful reproduction of Example 25. 3/22/16 PM Roush Tr. 154:6.

1032. Dr. Buschmann's batch #00 was chemically impure. This is apparent from the odd melting test behavior reported for this sample. Grünenthal did not observe a melting point at all for batch #00, contrary to what is required by Example 25. Dr. Buschmann agreed the melting point "was not measurable." 3/10/16 Buschmann Tr. 144:17-18. Instead, the lab notebook page shows "sintering" at 123 °C with decomposition. DTX 974; 3/15/16 Steed Tr. 55:14-56:10. Sintering is different from melting in that no liquid forms, instead the sample remains solid and the particles "merg[e] together" during heating. 3/15/16 Steed Tr. 56:1-2. The melting point of tapentadol is expected to be about 200 °C. 3/15/16 Steed Tr. 63:23-25. The observed sintering at 123 °C, rather than any true melting point, "seems to indicate something that's very impure indeed." 3/15/16 Steed Tr. 56:9-10.

1033. Buschmann's batch #01 more closely follows Example 25, at least to the extent it starts with the appropriate (-23) starting material in step 3. 3/15/16 Steed Tr. 56:18-57:1; DTX 977. However, plaintiffs have not provided any XRPD data for batch #01. 3/15/16 Steed Tr. 57:2-3, 41:15-21. Grünenthal employee and '364 patent inventor, Dr. Gruss testified that he did not even know what Batch #01 was, and confirmed he did not have any polymorph test data for it. 03/11/16 Gruss Tr. 8:24-9:8.

1034. The melting point for the product recorded in Dr. Buschmann's lab notebook for batch #01 is 199.9-200.9 °C. 3/10/16 Buschmann Tr. 186:13-15; DTX 977. The melting point reported in Example 25 is 168-170°C. DTX 920 at 19:10. Dr. Buschmann testified that this was a typographical error. *See, e.g.*, 3/10/16 Buschmann Tr. 187:6-12.

1035. Dr. Buschmann's lab notebook also reports an optical rotation of -26.0°, which does not match what is disclosed in Example 25. 3/10/16 Buschmann Tr. 185:21-186:5; DTX 977. The optical rotation stated in Example 25 is -27.5° using conditions of c=0.97 methanol. DTX 920 at 19:11.

1036. Dr. Buschmann testified that the data recorded in Example 25 was not drawn from his lab notebook page recording the synthesis of Batch #01 but was a "compilation of all the information which was available. So it's not the 1 to 1 copy . . ." 3/10/16 Buschmann Tr. 188:4-13; *see also* DTX 920 at 19:29-30; DTX 977. He also could not identify who drafted Examples 24 or 25 or what information the drafter relied upon, stating "this was a compilation of all data we had at this point." 3/10/16 Buschmann Tr. 190:5-10.

1037. Dr. Buschmann was not able to identify the source of the information reported in Examples 24 and 25 of the '593 patent. 3/10/16 Buschmann Tr. 191:6-9; DTX 920 at 17:37-19:30. Nor was he able to identify a single lab notebook page or protocol where somebody at

Grünenthal followed the recipe exactly as is written in the third step of Example 25. 3/10/16 Buschmann Tr. 193:23-194:4.

1038. Dr. Bernstein does not know and has no opinion about how batch #00 was made. 3/21/16 Bernstein Tr. 267:22-268:2.

1039. Ignoring, the fact that Batch #00 was not synthesized according to Example 25 of the '737 patent as discussed above, it is more than likely that Batch #00 was impure. Dr. Gruss was hired by Grünenthal in May 2000. 3/11/16 Gruss Tr. 7:25. Batch #00 was synthesized in 1994. 3/10/16 Gruss Tr. 244:3-5; 3/10/16 Buschmann Tr. 26:10-27:5; PTX 345. But no Tapentadol batch was ever tested by XRPD or DSC for its polymorph determination until 2001, including Batch #00. 03/11/16 Gruss Tr. 34:13-17; 5/1/15 Dep. Tr. Lischke 122:8-11; PTX 511_T. No one can attest to where or in what conditions Batch #00 was kept in between that time. Dr. Buschmann left Grünenthal in 2002 and left batches #00 at Grünenthal but does not know where he left those samples. 3/10/16 Buschmann Tr. 196:7-15. Dr. Gruss doesn't remember where Batch #00 samples were taken from in order to conduct XRPD in 2001; who handed it to him; what color it was; who had been keeping it; or what storage conditions it was kept in for the seven years Batch #00 was allegedly somewhere within Grünenthal. 03/11/16 Gruss Tr. 34:13-35:7.

1040. It is more than likely that Batch #00 was not stored in an appropriate manner during the several years between its synthesis and testing. Samples of compounds at Grünenthal were not stored with consideration to maintaining polymorphic forms during the time between when tapentadol Batch #00 was synthesized and later tested by XRPD; "the focus was not on polymorphism, the focus, rather, was on chemical purity." 5/1/15 Dep. Tr. Lischke 112:23-113:21. Moreover, samples of tapentadol were even less likely to be stored under good

conditions, as Dr. Fischer testified "we all knew that [tapentadol] is a very [chemically] stable product, so I think there is no need to store it under good conditions." 3/26/15 Dep. Tr. Fischer 161:12-19.

1041. Regardless of storage conditions, Batch #00 should never have been used in 2001. Grünenthal's own normal practice was to "usually keep [samples] for five years…. So none of the chemical or – or pharmaceuticals are kept longer than that, say, at least in official use." 3/26/15 Dep. Tr. Fischer 227:14-22. As Dr. Fischer explained: "If you today would make a batch of tapentadol then – if you make it now, today, then after five years, you cannot use it any longer." 3/26/15 Dep. Tr. Fischer 227:23-228:2. Yet Batch #00 was being tested seven years after it was initially synthesized.

2. Mueller's reproductions were not faithful reproductions and she didn't have the right experience

1042. Marita Mueller, a chemical lab assistant at Grünenthal, was asked to replicate Example 25 of EP 639475 several times over the course of several years. 4/10/15 Dep. Tr. Mueller 17:17-24, 98:8-12; 03/16/16FF Matzger Tr. 96:10. Example 25 of EP '475 is the equivalent of Example 25 in the '737 patent. 03/16/16FF Matzger Tr. 96:1-17. Ms. Mueller had limited knowledge of tapentadol before attempting those replications, and received limited guidance on how to perform the procedure. Marita Mueller does not have a Ph.D. 4/10/15 Dep. Tr. Mueller, 12:24-13:1; 3/11/06 Tr. Gruss 49:13-15; 3/15/16 Steed Tr. 42:23-43:3.

1043. In 2002, Dr. Griebel, Ms. Mueller's supervisor, tasked her with replicating Example 25 of EP Patent 693475 even though Ms. Mueller did not have any previous experience with tapentadol and did not have any familiarity with any attempts to synthesize tapentadol. 4/10/15 Dep. Tr. Mueller, 20:3-5, 21:4-15, 25:10-26:20, 36:13-25; 37:6-10; 48:12-23, 48:25-49:1, 61:88-16; 3/15/16 Steed Tr. 43:4-8. Ms. Mueller knew of tapentadol but was unaware of its

chemical structure. 4/10/15 Dep. Tr. Mueller, 24:7-12. No one other than Dr. Griebel ever discussed replication of Example 25 with Ms. Mueller, including any of the co-inventors. 4/10/15 Dep. Tr. Mueller, 21:20-24; 22:1-24; 23:11-23; 37:15-17; 3/11/06 Tr. Gruss 48:14-18. And when she actually attempted to replicate Example 25, she worked alone, without the help or aid of anyone. 4/10/15 Dep. Tr. Mueller, 37:22-38:12. Consequently, Ms. Mueller did not faithfully replicate the procedures set out in Example 25.

3. **Ms. Mueller's first attempt – Bu322-1-1**

1044. Ms. Mueller's first attempt to replicate Example 25 was labelled as GB-Bu 322-1-1. 4/10/15 Dep. Tr. Mueller 47:25-48:2, 48:5-14; PTX 567_T at 19. That experiment was conducted September 5, 2002. 4/10/15 Dep. Tr. Mueller, 48:12-23, 48:25-49:1; PTX 567_T at 19. When she conducted GB-Bu 322-1-1, Ms. Mueller did not have "any other lab notebook entries or other instructions, other than the patent." 4/10/15 Dep. Tr. Mueller 50:8-12.

1045. Prof. Steed analyzed the lab notebooks documenting Ms. Marita Mueller's attempts to reproduce Example 25 and confirmed her attempts were not faithful reproductions. 3/15/16 Steed Tr. 41:22-42:7; DTX 1003 at 14-15; *see also* 3/16/16FF Matzger Tr. 71:1-4. In her hands, tapentadol did not crystalize as described in Example 25: "when following the teachings of the patent, nothing crystallized out. The procedure just quite simply didn't work." 3/15/16 Steed Tr. 42:8-13.

1046. Prof. Steed identified a number of mistakes that Ms. Mueller made in attempting to reproduce Example 25. 3/15/16 Steed Tr. 44:8-16. Ms. Mueller never characterized her starting material—(-23 or BU 351-1-1)—for step 3 of Example 25 for chemical purity. 3/15/16 Steed Tr. 44:22-45:1; 4/10/15 Dep. Tr. Mueller 57:21-25, 59:15-23; 60:15-19. Nor did Ms. Mueller attempt to purify Bu 351-1-1 prior to using it as starting material, and thus she did not

rule out the possibility that impurities were being carried forward throughout the procedure and affecting the outcome. 4/10/15 Dep. Tr. Mueller 61:2-6.

1047. Ms. Mueller's notebooks do not indicate that she properly neutralized—made alkaline—the HBr acid. As Prof. Steed explained, Ms. Mueller used sodium hydrogen carbonate to neutralize but did not record in her notebook the resulting pH thus failing to confirm that it was a pH of 8.0, as appropriate. DTX 1003 at 14; 3/15/16 Steed Tr. 45:24-46:19. In contrast, the UW scientists reported obtaining a pH of 8.0 at this point in the procedure. DTX 298 at 3; 3/15/16 Steed Tr. 32:15-20. A POSA would know that the HBr acid without a proper alkaline pH could result in a bromide impurity in the final product. 3/15/16 Steed Tr. 46:20-47:1. Dr. Buschmann agreed that one following Example 25 should use an alkaline pH, for example a pH of 8.0. 3/10/16 Buschmann Tr. 177:16-22.

1048. The extraction step is another source of error in Ms. Mueller's work. As Prof. Steed explained, this is a manual process that involves a separation of two liquid layers—one organic and one aqueous—using a separation funnel. This is a manual process that someone unaccustomed to the procedure may not carry out properly. 3/15/16 Steed Tr. 47:2-48:1. Even a very small amount of water that remains in the organic layer could result in a bromide impurity in the final product. 3/15/16 Steed Tr. 48:2-10.

1049. Example 25 further teaches how to reduce contamination with a drying step to remove excess water that may be present after extraction. 3/15/16 Steed Tr. 48:11-15. The drying step is done by adding the drying agent, sodium sulfate, to the organic solution and swirling for several minutes so that the sodium sulfate has an opportunity to absorb and remove the water. 3/15/16 Steed Tr. 48:16-25. Ms. Mueller's notebook shows that she "filter[ed] the extract over sodium sulfate." DTX 1003 at 14; 3/15/16 Steed Tr. 16-25. As Prof. Steed explained "[t]here's a

big difference between filter over and dry over. 3/15/16 Steed Tr. 48:22-49:5. "Filtering over" means pouring the dichloromethane solution over the drying agent and it filters straight through so the contact time between the potentially water-containing solution and the drying agent is far less than what is called for in Example 25. 3/15/16 Steed Tr. 48:22-49:4. The organic solution if not dried properly, will expose the final product to a solution "laced with impurities, particularly sodium bromide. But also any other trace impurities that have been generated in this very aggressive reaction." 3/15/16 Steed Tr. 49:5-11.

1050. Ms. Mueller also failed to premix TMCS and water in the final crystallization step of Example 25. 3/15/16 Steed Tr. 49:12-29. She added the water directly to the butanone solution containing the tapentadol free base, and then added the TMCS to the butanone solution. 3/15/16 Steed Tr. 49:20-25; DTX 1003 at 14; 4/10/15 Dep. Tr. Mueller 80:25-81:15. As a result, the TMCS and water were not given an opportunity to react with each other to generate hydrochloric acid. 3/15/16 Steed Tr. 50:1-8. Instead, the TMCS had an opportunity to react directly with tapentadol. Failure to pre-mix the TMCS and water is "another way to generate impurities," and it is not the procedure taught in Example 25. 3/15/16 Steed Tr. 50:1-11.

1051. Example 25 teaches that after the "TCMS/water" mixture is added to the butanone solution of tapentadol free base that tapentadol hydrochloride (-21) "crystallized out." DTX 752 at 19:65; 3/15/16 Steed Tr. 50:16-19. This did not happen in Ms. Mueller's attempted reproductions, showing that she had not followed the procedure properly. 3/15/16 Steed Tr. 50:15-19. Ms. Mueller was forced to "improvise" and used an ice bath with stirring for 90 minutes to get some material to crystallize out. 3/15/16 Steed Tr. 50:20-51:1; DTX 1003 at 14; 4/10/15 Dep. Tr. Mueller 63:14-24, 65:19-23, 64:25-65:2, 65:5-11, 66:4-19. But these additional steps are not present in Example 25.

1052. As a result of her mistakes, the product Ms. Mueller obtained in her first attempted reproduction was "mustard yellow." 4/10/15 Dep. Tr. Mueller, 68:6-9; 78:1-5; PTX 385_T at 14; DTX 1003 at 14; 3/15/16 Steed Tr. 51:1-5. The yellow color indicated an impure product. 3/15/16 Steed Tr. 51:1-5.

1053. Tapentadol hydrochloride is a white solid. Grünenthal's internal documents "show that the material obtained as the product of Example 25 of the '737 patent was a white solid." 3/16/16FF Matzger Tr. 97:19-98:2; DTX 1202; DTX 1206. Dr. Buschmann recalled that tapentadol hydrochloride is a "white powder" and testified that he could not "remember that I have seen any yellow tapentadol hydrochloride." 3/10/16 Buschmann Tr. 128:4-18; DTX 1414 at 7. As Dr. Matzger explained "[I]n the most basic organic chemistry lab course, we tell people that, you know, your material, it should be white, and if it's off color, you need to repurify it, you need to keep going. So color in an otherwise colorless compound is an indicator of impurities." 3/16/16FF Matzger Tr. 96:11-97:3; *see also* 3/15/16 Steed Tr. 51:1-5.

1054. H-NMR and C-NMR detect hydrogen and carbon atoms, respectively. 3/15/16 Steed Tr. 20:22-21:13. Accordingly, these techniques will not detect inorganic impurities that do not contain hydrogen or carbon, for example bromide. 3/15/16 Steed Tr. 20:22-21:13, 22:23-23:3. The importance of bromide as a potential impurity is set forth in ¶ 77. And yet, Ms. Mueller "never thought about" checking for bromide. 4/10/15 Dep. Tr. Mueller 82:12-22. Ms. Mueller "never measured the purity" of the product resulting from Bu 322-1-1. And that product cannot now be tested for purity because "it no longer exists. It's been used up." 4/10/15 Dep. Tr. Mueller 72:21-73:1.

a. **Ms. Mueller's second attempt – Bu322-1-2**

1055. In November 22, 2002, Ms. Mueller made a second attempt at replicating Example 25, labeled "GB-Bu 322-1-2 (BN 200)." 4/10/15 Dep. Tr. Mueller 97:16-19, 98:1-12;

PTX 385 at 15. She made similar mistakes including failing to premix TMCS and water (4/10/15 Dep. Tr. Mueller 101:4-12, 101:15-21) and did not obtain crystals as described in Example 25 so she had to improvise a series of steps to obtain any product at all. 4/10/15 Dep. Tr. Mueller 101:8-21, 102:4-11, 103:5-15, 104:10-23; PTX 385; PTX 385_T. Ms. Mueller determined that the product was "contaminated" and the attempt was abandoned. 4/10/15 Dep. Tr. Mueller 106:8-14, 107:1-10.

b. **Ms. Mueller's third attempt – Bu322-1-3**

1056. On November 29, 2002, Ms. Mueller made a third attempt to reproduce Example 25, labeled as Bu322-1-3. DTX 1003 at 15; 4/10/15 Dep. Tr. Mueller 110:18-11:2; PTX 385_T at 15. In addition to starting with the wrong amount of starting material—1.23 grams of (-23) rather than 4.3 grams—this attempt had the same mistakes as the first attempt and resulted in a discolored "beige" product. 3/15/16 Steed Tr. 51:17-52:7; DTX 1003 at 15; 3/16/16FF Matzger Tr., 99:7-14; 4/10/15 Dep. Tr. Mueller, 111:14-18, 111:20-22, 116:18-25; PTX 385_T at 15. Additionally, the reported "melting point is rather broad and lower than was reported for the original material that forms the basis of Example 25." 3/16/16FF Matzger Tr., 99:7-14.

1057. For 322-1-3, Ms. Mueller used a starting material from a different batch than the starting material used in conducting 322-1-1. 04/10/15 Dep. Tr. Mueller, 112:7-17. But as was the case for 322-1-1, "no purity was analyzed" for the starting material. 04/10/15 Dep. Tr. Mueller 112:21-25, 113:2-7.

c. **Ms. Mueller's fourth attempt – PG1026**

1058. Ms. Mueller made another attempt to reproduce Example 25 in 2009 (about 7 years after her first three attempts). DTX 1034; 3/15/16 Steed Tr. 52:20-53:5; 4/10/15 Dep. Tr. Mueller 128:23-24, 129:1-4, 130:1-17; PTX 1480; PTX 1487. This experiment was similarly not a faithful reproduction of Example 25, but this attempt was worse since she started with the

wrong starting material—a hydrobromide salt—rather than the hydrochloride salt (-23) identified in the example. 3/15/16 Steed Tr. 53:6-11; 4/10/15 Dep. Tr. Mueller 136:1-15. She was unaware of the origin of the starting material. 4/10/15 Dep. Tr. Mueller 139:11-18. She followed the same flawed procedure used in her first and third attempted reproductions, making similar mistakes that resulted in a cream-colored solid and "[t]he melting point again is somewhat broader than was found in the result of Example 25" indicating the presence of impurities. DTX 1034 at 3; 3/15/16 Steed Tr. 53:12-24; 3/16/16FF Matzger Tr. 102:23-103:5; 4/10/15 Dep. Tr. Mueller 138:23-139:2; *see also* 4/10/15 Dep. Tr. Mueller 137:18-20 (failure to premix TCMS/water) and 137:25-138:2, 138:16-21 (ice bath and stirring added required to get crystal). Once again, "there was no testing of purity that was ordered." 4/10/15 Dep. Tr. Mueller 139:3-9. And no NMR analysis was conducted either. 4/10/15 Dep. Tr. Mueller 146:5-7.

1059. X-ray diffraction patterns of PG 1026-001 also indicate the presence of impurities. DTX 1317 presents the X-ray patterns of Form A, (green), Form B (red), and PG 1026-001 (blue). 3/16/16FF Matzger Tr. 103:6-20. The pattern for PG 1026-001 varies from the Form B pattern at certain points, such as at 20.2 and 22.0. 3/16/16FF Matzger Tr. 104:7-11, 104:17-21; DTX 1317. As Dr. Matzger explained "[t]his sort of behavior is a telltale sign of impurity incorporation. So what happens is, the impurities go into the lattice and they expand it selectively in some dimensions and you get shifting of just some of the peaks of the powder x ray diffraction." 3/16/16FF Matzger Tr. 104:12-16.

C. Form B samples that persist at room temp. are stabilized by impurities.

1. Form A is the stable form that usually exists at room temp.

1060. As Grünenthal's own internal reports state there was "no evidence, that a third modification, a solvate or an amorphous form [of tapentadol] has ever occurred," essentially there are only two possible polymorphs—Forms A and B. DTX 1242 at 22; DTX 1062 at 1-2;

DTX 1075 at 1; 3/21/16 Bernstein Tr. 274:14-19. In fact, Dr. Fischer summarizes a number of experiments and concludes "the existence of a third polymorph based on the current data is most unlikely." DTX 1242 at 22; *see also* 3/15/16 Steed Tr. 73:13-14; 3/21/16 Bernstein Tr. 288:1-4; DTX 1158 at 7, 10; DTX 1242 at 20; DTX 1008 at 3, 6-7. Dr. Bernstein also testified that he had not seen any evidence of a third form of tapentadol hydrochloride. 3/21/16 Bernstein Tr. 287:17-22. SSCI also confirmed that there are only two polymorphs. 3/11/16 Gruss Tr. 19:20-23; DTX 1279.

1061. Of the two possible forms of tapentadol, Form A is the stable form at room temperature and Form B is a metastable form. DTX 1158 at 2; DTX 1062 at 1; DTX 1075 at 1; 3/21/16 Bernstein Tr. 268:3-6, 271:20-22, 277:11-20; 3/10/16 Buschmann Tr. 201:23-202:2; 3/15/16 Steed Tr. 17:22-18:8, 65:2-18; 3/11/16 Gruss Tr. 20:7-10, 23:4-8; 5/08/15 Dep. Tr. Struck 138:22-139:2; 3/26/15 Dep. Tr. Fischer 60:12-25. Form B is unstable and will not normally persist at room temperature. As Prof. Steed explained:

> It's what we scientists call an enantiotropic pair. So one form is stable at room temperature; one form is stable at high temperature. And there's a very fast conversion between them such as you see that conversion happening on the time scale of the experiment. So a matter of a few minutes. So, in other words, Form B simply doesn't persist at room temperature, it's unstable.
> (3/15/16 Steed Tr. 59:1-7).

1062. As such, it was difficult to obtain pure Form B while Form A "can be synthesized reproducibly." 3/16/16FF Matzger Tr. 88:7-21, 84:25-85:4; DTX 1242 at 13. Grünenthal's own internal documents reported they had been "synthesizing tapentadol hydrochloride and they find that the product from the synthesis is Form A. This is the result they were getting in-house." 3/16/16FF Matzger Tr. 87:18-22; *see also* DTX 1075 at 1, 8.

1063. Obtaining pure Form B proved very difficult to do because Form A is the inherently more stable and natural form for this compound. "A variety of studies were performed

in hopes of producing a stable sample of pure Form B." DTX 1279 at 3. "In each case, Form A was produced." DTX 1279 at 3. For example, SSCI tried to isolate Form B by dissolving Form A in various solvents followed by centrifuging under vacuum but even that extreme step still resulted in some Form A. 3/11/16 Gruss Tr. 25:1-12; DTX 1279 at 3. SSCI even milled Form A at sub-ambient temperatures in a "cryo miller" and also milled Tapentadol while it was submerged in liquid nitrogen, but these techniques still resulted in some Form A. 3/11/16 Gruss Tr. 25:25-26:8; DTX 1279 at 3-4. SSCI applied a hydraulic press to Form A at 5000 PSI for several days, and that still resulted in Form A. 3/11/16 Gruss Tr. 26:9-14; DTX 1279 at 3-4; *see also* 3/16/16FF Matzger Tr. 85:14-22; DTX 1088; 3/10/16 Buschmann Tr. 200:17-22; DTX 1087 at 18-20; DTX 1001 at 15-16.

1064. After trying extreme techniques to try to make Form B Tapentadol, SSCI gave up and reported to Grünenthal just how difficult it was to make. SSCI reported in 2001: "[t]o date, the only repeatable method for making Form B involves milling Form A for a least 15 minutes, to get a sample that is a mixture of Form A and B based on XRPD…, then heating this mixture in a TGA to 125°C for a half hour." 3/11/16 Gruss Tr. 26:21-27:7; DTX 1279 at 3-4.

2. **Normally Form B converts to Form A at Room Temperature**

1065. While it was difficult to produce pure Form B at room temperature, Form A when heated would convert to Form B and then convert back to Form A in ambient temperatures. 3/16/16FF Matzger Tr. 86:23-87:8; 3/26/15 Dep. Tr. Fischer 90:21-91:15; 3/21/16 Bernstein Tr. 269:23-270:5, 271:10-14; DTX 1062 at 1; DTX 1087; DTX 1242; DTX 1001 at 18, Table 10; DTX 1075 at 3-4; DTX 1279 at 3-4. XRPD patterns showed that Form A converted to Form B when heated to 75 °C and converted back to Form B upon cooling to room temperature overnight. DTX 1001 at 18, Table 10; 3/21/16 Bernstein Tr. 269:6-270:2, 271:10-14. A 2001 internal Grünenthal memo and 2005 presentation authored by Dr. Fischer detailed that Form A

converts to Form B at temperatures greater than at least 40°C or alternatively by "grinding/milling." DTX 1062 at 1; DTX 1242 at 5; 3/21/16 Bernstein Tr. 274:20-25.

1066. Dr. Steed explained that internal Differential Scanning Calorimetry ("DSC") and variable temperature XRPD experiments show that Form B will convert to Form A at room temperature unless something is stopping it. 3/15/16 Steed Tr. 57:14-59:7, 61:11-64:23; 65:13-18; DTX 1001 at 18; DTX 1243 at 9.

1067. The behavior of Forms A and B is explained by Prof. Englert at the University of Aachen whom Grünenthal commissioned to use single crystal X-ray diffraction studies to help explain the nature of the transition between the two forms. DTX 993; 3/15/16 Steed Tr. 59:8-60:4. He reported that the only difference between Form A and Form B is a slight rotation around one carbon-carbon bond; Dr. Fischer later confirmed this fact. 3/15/16 Steed Tr. 60:5-19; DTX 993 at 2-3; DTX 1242 at 6. Dr. Englert was able to calculate the energy barrier for this transition—5kcal/mole—which is very low, resulting in an easy transition between the two forms at room temperature. 3/15/16 Steed Tr. 60:19-61:1; DTX 993 at 3. In light of this evidence, Prof. Steed concluded: "It was a very easy transition. It didn't involve breaking or making any bonds. And so it wasn't surprising that it would happen so readily and so Form B would transform back to A as soon as you cool it." 3/15/16 Steed Tr. 61:2-7.

3. **Form B is stabilized by Impurities**

1068. A POSA would expect the synthesis of Example 25 to result in Form A because that is the more stable form at room temperature and Form B converts Form A at room temperature unless it contains impurities. 3/15/16 Steed Tr. 17:22-18:8.

1069. Dr. Bernstein testified that impurities can "influence the result of a crystallization" and that "impurities definitely can influence which direction a crystallization goes." 3/21/16 Bernstein Tr. 256:24-257:18. If Form B does not convert to Form A at room

temperature, there is something that is preventing that conversion which should otherwise happen. 3/21/16 Bernstein Tr. 271:23-272:3. Dr. Bernstein testified that there must be something different between the samples of Form B that convert to Form A at room temperature and those that persist as Form B. 3/21/16 Bernstein Tr. 270:3-24.

1070. Grünenthal looked into the question of why Form B sometimes persisted at room temperature and found that impurities are likely to play a role in preventing the conversion to Form A. 3/21/16 Bernstein Tr. 272:3-14.

a. **Grünenthal Internal Reports**

1071. Internal Grünenthal documents show that in-house scientists extensively discussed the role of impurities stabilizing Form B. The results of Grünenthal's investigation led it to believe that impurities would result in Form B; "we had this impression that certain amount of impurities could help." 3/26/15 Dep. Tr. Fischer 158:16-22. Conversely, there is no evidence that would indicate impurities could stabilize Form A at room temperature. 3/21/16 Bernstein Tr. 272:15-24.

1072. In 2003, Dr. Andreas Fischer, prepared a Research Report entitled "Summary of Polymorphism Investigations of CG5503" that investigated the effect of impurities. DTX 1158. Then, in 2005 he presented a slide deck presentation titled "CG 5503 – Summary Polymorphism" also addressing impurities. DTX 1242 at 1, 18; 3/21/16 Bernstein Tr. 277:3-10. In his 2003 Research Report and 2005 presentation, Dr. Fischer lists possible explanations for why Form B samples may persist at room temperature and not convert to Form A. DTX 1158 at 7; DTX 1242 at 18; 3/21/16 Bernstein Tr. 280:2-6.

1073. Two of the explanations relate to impurities: a bromide impurity or byproduct and degradation product impurities. DTX 1158 at 7; DTX 1242 at 18-21; 3/21/16 Bernstein Tr. 280:7-15; 3/15/16 Steed Tr. 69:25-70:3, 72:18-73:16. The scientists recognized that impurities

likely stop Form B from converting to Form A as it otherwise would. 3.15.16 Steed Tr. 66:20-67:10. A theory suggesting that particle size played a role was rejected. DTX 1242 at 20. The possibility of a third polymorph was also quickly rejected. *See* ¶ 1060.

1074. Dr. Fischer suggests that "[c]rystallation [sic] of the corresponding bromide salt of CG5503 yields in an isotypic structure to the B modification of the chloride salt." DTX 1158 at 7; DTX 1242 at 21; 3/21/16 Bernstein Tr. 280:20-25; 3/15/16 Steed Tr. 70:17-24. "Isotypic" means that the structure of the bromide salt is the same as the Form B chloride salt, increasing the likelihood that bromide could replace chloride in the crystal structure. 3/15/16 Steed Tr. 70:20-22; 3/21/16 Bernstein Tr. 281:14-21. Dr. Fischer concluded "[l]ow amounts of bromide are expected to affect the transition temperature of CG 5503 to lower temperature." DTX 1242 at 21. And bromide is particularly relevant here because it is present in excess as HBr acid during step 3 of Example 25, so that if the other steps in the procedure are not followed accurately then that alone explains why Form B could be accidentally prepared when the Example 25 procedure naturally results in Form A. 3/15/16 Steed Tr. 70:9-13.

1075. Dr. Bernstein testified that "if [Form B] is due to impurities, you have to show which impurities and what the level is," which is exactly what Grünenthal did. 3/21/16 Bernstein Tr. 284:12-18; DTX 1158 at 9; DTX 1242 at 19. Grünenthal conducted a series of experiments in which it "spiked batches with different amounts of impurities," and it determined that two impurities, BN300 and Bu351, stabilized Form B when present at certain levels, concluding that "[s]ystematic analysis of the batches are pointing to a correlation of impurity – Form B production (Table 1)." DTX 1158 at 8-9; 3/21/16 Bernstein Tr. 285:25-286:6, 287:7-16; 3/15/16 Steed Tr. 62:13-64:23; DTX 1243 at 9.

1076. From the data generated by Grünenthal and reported in Dr. Fischer's Research Report and slide deck presentation only CEPM1a and CEPM2a resulted in pure Form B. DTX 1158 at 8; DTX 1242 at 19. Predictably, these two samples had the highest levels of BN 300 and Bu351, while the samples with lower impurity levels resulted in at least some Form A. DTX 1158 at 8; DTX 1242 at 19; 3/15/16. Steed Tr. 67:19-69:6. Thus, Grünenthal itself concluded that "[i]mpurities affect the formation of the unfavoured modification Form B." DTX 1242 at 19; 3/15/16 Steed Tr. 69:7-14; 3/11/16 Gruss Tr. 73:4-12.

b. **Grünenthal's analysis of SSCI results**

1077. In a September 2001 status report regarding SSCI's polymorph screen of tapentadol, Grünenthal explained that conversion of Form B to Form A at room temperature "could depend on the impurities profile." PTX 1486 at 1; *see also* DTX 1062 at 12; 3/21/16 Bernstein Tr. 275:7-14; 3/10/16 Buschmann Tr. 203:1-7. This report also contains a slide stating only one theory to explain the inhibited transformation of Form B to A: "It might be due to impurities which inhibit the transformation from Form B to Form A." DTX 1062 at 12; PTX 1486 at 12; *see also* 3/21/16 Bernstein Tr. 275:15-25.

c. **Crystallics Reports**

1078. Grünenthal contracted with Crystallics in 2003 to study the crystallization of tapentadol hydrochloride. (DTX 995). Grünenthal asked Crystallics to compare "the different impact of the different impurities" on the solid form of tapentadol. DTX 995 at 10, 23; 3/11/06 Gruss Tr. 32:7-16; 3/21/16 Bernstein Tr. 290:14-17. Crystallics generated a Final Report dated May 2003. DTX 995. Crystallics confirmed that Grünenthal recognized the effect impurities could have: "Grünenthal has previously indicated that the polymorphic form of CG5503 is affected by the amount of the impurities, GRT4045Y and GRT0912Y, in the mixture upon crystallization." DTX 995 at 10; 3.15.16 Steed Tr. 71:15-72:4; 03.11.06 Gruss Tr. 31:22-32:6.

The upper table on page 23 of the Crystallics Final Report shows the polymorphs that resulted when impurities were added to the solution before crystallization. DTX 995 at 23; 3/21/16 Bernstein Tr. 290:20-291:11. The Crystallics report concluded that "[h]igher amounts of GRT0912Y were observed to have a larger influence of the formation of polymorph B than GRT4045Y." DTX 995 at 10; 3/15/16 Steed Tr. 72:5-14; 03/11/16 Gruss Tr. 32:19-24.

1079. Form A thus always and necessarily results from the synthesis of tapentadol hydrochloride described in Example 25 of the '737 patent. Claims 1-3 of the '364 patent are inherently anticipated and invalid. (3.15.16 Steed Tr. 73:25-75:3).

III. ASSERTED CLAIMS OF THE '364 PATENT ARE INVALID AS OBVIOUS

A. A POSA would have been motivated to search for crystal forms of tapentadol including the most stable form.

1501. The '737 patent states that the molecules disclosed therein were intended to have analgesic effect which is suitable for the treatment of pain. DTX 752 at 1:53-54; 3/15/16 Steed Tr. 76:15-7:1. Tapentadol hydrochloride was also listed as an analgesic in a 2002 World Health Organization publication. DTX 260 at 72; 3/22/16 Bernstein Tr. 20:12-21:17.

1502. The '737 patent does not expressly disclose the crystal structure of tapentadol hydrochloride, but confirms that it can be made in a crystalline form. 3/15/16 Steed Tr.77:3-6.

1503. A POSA would have been motivated to screen tapentadol hydrochloride because screening for polymorphs is a routine part of drug development. 3/15/16 Steed Tr. 77:7-10. Such screens were routine at least because the Food and Drug Administration ("FDA") had issued guidelines as early as 1987 indicating that "[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs." DTX 290 at 37; 3/15/16 Steed Tr. 77:11-19. Dr. Buschmann testified that once tapentadol hydrochloride entered clinical development "it was considered important also to take consideration of the so-called solid phase of the compound

intended for oral use." 3/10/16 Buschmann Tr. 77:17-22. This work included 'investigat[ing] that hydrochloride salt [of tapentadol] if different polymorphs may exist." 3/10/16 Buschmann Tr. 77:23-78:4. Dr. Gruss agreed. 3/11/16 Gruss Tr. 77:1-19.

1504. Dr. Stephen Byrn's article "Pharmaceutical Solids: A Strategic Approach to Regulatory Consideration," published in 1995 states "[i]nterest in the subject of pharmaceutical solids stems in part from the FDA's drug substance guideline that states 'appropriate' analytical procedures should be used to detect polymorphic, hydrated or amorphous forms of the drug substance." DTX 755 at 1; 3/15/16 Steed Tr. 78:23-79:18; 3/22/16 Bernstein Tr. 23:11-23. Dr. Buschmann agrees "there was certain guidance in the ICH Guidelines or industry from the FDA how this polymorph form should be considered in a development program." 3/10/16 Buschmann Tr. 161:19-162:1.

1505. When SSCI was hired to perform polymorph screens by Grünenthal, the agreement provided a "Rationale" for the polymorph screen: "This study is an initial investigation of the existence of polymorphs as recommended by the ICH Q6A flow chart. The complete screen is designed to provide as complete a picture as possible of the polymorphs of BN200." DTX 1294 at 8. The ICH Q6A flow chart is similar to the polymorph decision tree in Fig. 1 of the prior art Byrn article. DTX 1294 at 10; DTX 755 at 2; 3/22/16 Bernstein Tr. 27:7-12, 27:25-28:3.

1506. Regardless of the FDA guidelines, it would have been important to know if tapentadol was polymorphic "not only [for] the regulatory bodies, it was important for any further developments that, to have knowledge of solid form characteristics." 3/10/16 Buschmann Tr. 162:16-25.

1507. There was also guidance in the literature that the more stable form of a drug was preferred in a dosage form. DTX 930 at 2; 3/15/16 Steed Tr. 84:3-20. The more stable polymorph is the obvious form to start with when developing a dosage form. 3/15/16 Steed Tr. 83:10-20. This is because "chances are you will encounter the fewest problems in delivery and storage and formulation and what have." 3/22/16 Bernstein Tr. 14:19-21. Using the more stable form generally increases the shelf life of a product, decreases decomposition, and minimizes the risk of converting into another polymorphic form; which are all desirable properties for a solid pharmaceutical composition such as tapentadol. 3/22/16 Bernstein Tr. 16:4-8.

1508. Dr. Bernstein agreed with the statement in his "Polymorphism – A Perspective" article that "[m]any pharmaceutical companies seek to identify and then develop the most stable form of an active pharmaceutical ingredient." PTX 1037 at 4; 3/22/16 Bernstein Tr. 12:23-13:5. While "occasionally" there may be reasons to use a less stable form: material handling properties or intellectual property issues, Dr. Bernstein agreed that none of those issues are present for tapentadol. PTX 1037 at 4; 3/22/16 Bernstein Tr. 13:5-14:15.

1509. "Polymorph A has some technical advantages over Polymorph B. […] One of the advantages is that it is at room temperature thermodynamic more stable than Polymorph B." 3/26/15 Dep. Tr. Fischer, 60:12-25. Generally, "[f]rom a technical point of view, you would like to see the most stable polymorph in our chemical synthesis process or in the manufacturing process." 3/26/15 Dep. Tr. Fischer 61:1-5. Having the most thermodynamically stable polymorph shows "consistency of the manufacturing process." 3/26/15 Dep. Tr. Fischer 61:9-19.

1510. By 2000, Grünenthal generally understood that pharmaceutical companies are supposed to "take consideration of polymorphism when they are developing pharmaceutical compounds." 3/11/16 Gruss Tr. 77:1-19.

B. Grünenthal hired SSCI to conduct standard polymorph screen

1511. Dr. Gruss looked to third party companies to conduct routine polymorph screening, as Grünenthal "initiated systematic polymorphism investigations with an external company." 03/10/16 Gruss Tr. 236:12-24, 237:18-22. In particular, Grünenthal hired SSCI "to study a systematic polymorphism, to perform systematic polymorphism studies." 3/11/16 Gruss Tr. 15:6-10; 5/1/15 Dep. Tr. Lischke 20:6-15, 21:4-8, 29:1-3; 3/15/16 Steed Tr. 81:3-8; 3/10/16 Buschmann Tr. 200:14-22. Dr. Bernstein testified that tapentadol was the first time Grünenthal had addressed a polymorph issue. 3/22/16 Bernstein Tr. 9:5-9.

1512. Grünenthal signed an agreement with SSCI to conduct a polymorph screen of tapentadol hydrochloride on May 14, 2001. DTX 1294 at 1, 6; 3/22/16 Bernstein Tr. 26:12-15. The agreement contains a list of "Goals." DTX 1294 at 8. The second Goal is to "Carry out a polymorph screen, generating approximately 50-70 solid samples, analyze by XRPD." DTX 1294 at 8; 3/22/16 Bernstein Tr. 27:21-24. This is not a large number. Dr. Gruss admitted that 97 experiments are "not so much;" and that for a person in Dr. Gruss's field it would be part of the "day-to-day work routine." 03.11.16; Tr. Gruss 30:10-25.

1513. Essentially, the purpose of the SSCI investigation was to discover forms of tapentadol in addition to Forms A and B. 3/26/15 Dep. Tr. Fischer 101:5-16; DTX 1001 at 5; DTX 1242 at 22; DTX 1087 at 16.

1. **Polymorph screen is routine as of the priority date**

1514. The methods and procedures by which to conduct a polymorph screen were considered routine and well known to a POSA, including to Dr. Bernstein and Dr. Gruss. 3/15/16 Steed Tr. 78:20-22.

1515. Dr. Gruss understood that polymorph screening was a common technique and meant using different common solvents and temperatures to test for polymorphs. "Polymorph

investigation is to apply various parameters on the crystallization like temperature ranges, like various solvents to extend as broad as possible range of investigations in order to understand and characterize the compounds or the compound under consideration." 03/10/16 Gruss Tr. 228:15-21.

1516. Dr. Bernstein authored an article entitled "Polymorphism – A Perspective" that states "[c]rystallization from solution is one of the first laboratory skills that chemists acquire, and applying variations to the conventional methods has been the traditional strategy in the search for polymorphs." PTX 1037 at 3; 3/22/16 Bernstein Tr. 10:11-16.

1517. Dr. Bernstein used a demonstrative similar to Fig. 1 in his "Polymorphism – A Perspective" article to describe the time frames necessary for certain types of experiments that may be used to find a polymorph. 3/21/16 Bernstein Tr. 215:9-216:4, 10:17-21; PTX 1037 at 4, Fig 1. This figure indicates that "Solvent-Mediated Experiments"—such as crystallizations from solvents—can be conducted in second, minutes, or hours. PTX 1037 at 4. The longer time frames—days or months—are associated with "Solid-State Experiments" which are not relevant to traditional solution crystallizations. PTX 1037 at 4.

1518. Dr. Bernstein wrote in his article about different categories of procedures that can be used for crystallization. First, he wrote about "traditional solution crystallizations" and the parameters that may be varied in such experiments. PTX 1037 at 4; 3/22/16 Bernstein Tr. 11:19-25. Dr. Bernstein then wrote about "[o]ther conventional (although not as widely used) methods of crystallization," including sublimation, crystallization from melt, freeze drying and spray drying. PTX 1037 at 4; 3/22/16 Bernstein Tr. 12:1-12. The article mentions a third category of advanced techniques. PTX 1037 at 63961; 3/22/16 Bernstein Tr. 12:17-22.

1519. In his 2002 book, "Polymorphism in Molecular Crystals," Dr. Bernstein wrote that "[o]ne traditional strategy for screening a compound for polymorphic behavior involves the trial of a variety of solvents and solvent mixtures." PTX 1041 at 271; 3/21/16 Bernstein Tr. 254:21-255:12. Dr. Bernstein admitted that conducting a polymorph screen is a traditional strategy in 2002, and he wrote in his book that "[o]ur understanding of the role and choice of solvent has improved considerably" as of 2002. 3/21/16 Bernstein Tr. 256:2-7; PTX 1041 at 271.

2. **SSCI followed Byrn and other prior art publications.**

1520. In fact, the choice of common solvents and techniques that should be used in polymorph screens had been identified in Dr. Stephen Byrn's article "Pharmaceutical Solids: A Strategic Approach to Regulatory Consideration," published in 1995. DTX 755.

1521. The Byrn article explains the appropriate steps to detect polymorphism. Figure 1 of the article is a "Flowchart/decision tree for polymorphs." DTX 755 at 2. The first question in the decision tree is "Polymorphs Discovered?" DTX 755 at 2; 3/22/16 Bernstein Tr. 24:8-18. To answer this question the paper states "Different Recrystallizing Solvents (different polarity) – vary temperature, concentration, agitation, pH." DTX 755 at 2; 3/22/16 Bernstein Tr. 24:19-22; 3/15/16 Steed Tr. 80:4-17. The figure also identifies techniques, including XRPD, that can be used to "Test for Polymorphs." DTX 755 at 2; 3/22/16 Bernstein Tr. 24:23-25.

1522. The Byrn article states that the "[t]he first step in the polymorphs decision tree is to crystallize the substance from a number of different solvents in order to attempt to answer the question: Are polymorphs possible?" DTX 755 at 2. The article specifically lists certain solvents to use in the recrystallization experiments: water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate. DTX 755 at 2; 3/15/16 Steed Tr. 80:18-81:2.

1523. SSCI was founded by Dr. Byrn who wrote the 1995 article describing how to conduct a polymorph screen. DTX 755 at 1; 3/22/16 Bernstein Tr. 23:6-10.

1524. Because SSCI was a known company that did polymorph screens, it was straightforward for Grünenthal to ask them to "produce as many new forms of CG5503 as possible." 3/11/16 Gruss Tr. 19:8-15. CG 5503 is one of the project codes for tapentadol hydrochloride. 5/1/15 Dep. Tr. Lischke 27:1-4. There is no evidence that Grünenthal provided any direction to SSCI about what screening techniques to use, other than typical and traditional techniques. In fact, Dr. Lischke did not have any involvement in helping develop any of the polymorph screens conducted by SSCI. 5/1/15 Dep. Tr. Lischke 29:4-8.

3. Following the procedures and using common solvents from prior art resulted in Form A

1525. SSCI provided a project update on June 6, 2001, about three weeks after SSCI and Grünenthal signed the agreement for the polymorph screen; further evidencing the routine nature of polymorphs screens. DTX 1294 at 6; DTX 1087 at 1. This project update contained the initial results from SSCI. DTX 1087; 3/22/16 Bernstein Tr. 28:14-16. The update states that the "CG5503 polymorph screen is currently in progress. To date, two polymorphs have been discovered." DTX 1087 at 16; 3/22/16 Bernstein Tr. 28:23-25. Those two polymorphs were forms A and B. DTX 1087 at 16; 3/22/16 Bernstein Tr. 29:1-5.

1526. In addition to the June 6, 2001 Project Update, SSCI also generated a "Final Report" dated November 6, 2001. Both reports contain the results of the polymorph screen. DTX 1087 at 18-19; DTX 1001 at 14-15; 3/15/16 Steed Tr. 81:9-25; 3/26/15 Dep. Tr. Fischer 104:17-23, 105:4-25. SSCI used eight of the nine solvents listed in the Byrn paper. DTX 1087 at 18-19, Table 3; DTX 1001 at 14-15, Table 3; DTX 755 at 2. The only solvent that SSCI did not use from the Byrn list is propanol, which is an isomer of isopropanol, which SSCI did use (identified

as "1-Propanol (IPA)" in Table 3. DTX 1087 at 18-19; DTX 1001 at 15. SSCI also used different cooling and evaporation conditions to conduct the screen. 3/15/16 Steed Tr. 83:1-5; DTX 1087 at 18-19.

1527. In each of these experiments, where solid was obtained, SSCI always got at least some Form A. DTX 1087 at 18-19; DTX 1001 at 14-15; 3/15/16 Steed Tr. 82:13-14; 3/22/16 Bernstein Tr. 30:6-110. Prof Steed was not surprised by these results because Form A is the stable form of tapentadol hydrochloride, testifying that "Form A is the only form that's stable at room temperature. So I would have been surprised if they hadn't found it." 3/15/16 Steed Tr. 82:17-19.

1528. Claims 1-3 of the '364 patent cover Form A tapentadol hydrochloride identified by certain peaks in its XRPD pattern. DTX 304 at 18:66-19:16; 3/15/16 Steed Tr. 82:22-83:3. A routine polymorph screen, like the one described in the Byrn article, would have revealed Form A of tapentadol hydrochloride. 3/15/16 Steed Tr. 83:4-13.

1529. Claim 25 of the '364 patent directed to a solid dosage form containing tapentadol hydrochloride Form A identified by certain peaks in its XRPD pattern "and at least one suitable additive or auxiliary substance. DTX 304 at 20:56-63; 3/15/16 Steed Tr. 83:14-19. A POSA would have been motivated to use Form A in a dosage form because that is the form that is stable at room temperature. This would be common sense choice because a POSA would not have wanted a form that might convert to another form. 3/15/16 Steed Tr. 83:20-84:2. Additionally, the '737 patent teaches exactly the same thing as the '364 patent regarding use of additives or auxiliary substances with tapentadol. DTX 304 at 4:18-51; DTX 752 at 5:44-66.

1530. Dr. Bernstein testified that no polymorph can ever be obvious even if a specific polymorph screening process is provided in the prior art because "it is not predictable." 3/22/16 Bernstein Tr. 23:1-5; 30:23-312; *see also* 3/22/16 Bernstein Tr. 31:13-19

1531. Dr. Bernstein agreed that forms A and B have the same bioavailability. 3/21/16 Bernstein Tr. 288:5-8; 3/22/16 Bernstein Tr.16:15-18. Grünenthal's solubility studies of forms A and B showed that their solubilities are very similar. (DTX 1158 at 14). Grünenthal also found that the dissolution curves for capsules containing form A or form B were "identical." DTX 1158 at 15. Dr. Bernstein agreed that solubility for forms A and B are "quite similar." 3/21/16 Bernstein Tr. 288:9-13. Grünenthal concluded, summarizing the solubility and dissolution data, that "an influence of the polymorphic form on the drug release of the finished product is most unlikely." DTX 1158 at 15.

1532. Dr. Bernstein agreed that "sometimes it's easier and sometimes it's more difficult" to find polymorphs. 3/22/16 Bernstein Tr. 8:25-9:4.

1533. A person of ordinary skill in the art ("POSA") to which the '364 patent is directed would be someone with a Ph.D. in chemistry or a subject like crystallography and crystallization science or someone with a lower degree but some years of industrial research or laboratory experience. 3.15.16 Steed Tr. 76:1-7.

C. Started with A and ended with A.

1534. As explained in paragraphs 1024-1029 above, Grünenthal's supposed invention described in Example 2 of the '364 patent and many of the other examples was simply to take Form A Tapentadol and run various routine chemical steps to end up with the same form of tapentadol, Form A. As Dr. Gruss testified at trial, the "purpose of the procedure [of Example 2 of the '364 patent] was to provide Form A" Tapentadol. 3/11/16 Gruss Tr. 55:22.

IV. THE '364 PATENT SPECIFICATION FAILS TO SHOW UTILITY

A. The Statement of Utility is Inherently Vague and Insufficient

2001. The 7,994,364 Patent's ("the '364 Patent") lone contention of utility is the alleged stability of Form A. (DTX 304.) There is no other contention of utility set forth in Plaintiffs' discovery responses, Plaintiffs' portion of the Pre-trial Order, or their Pre-Trial Brief. *See* Plaintiffs' Pretrial Brief (ECF # 359) at 24; Joint Pretrial Order (ECF # 408) at ¶¶ 717-720

2002. The '364 patent states "Crystalline Form A according to the invention has the same pharmacological activity as Form B but *is more stable under ambient conditions*. It can be advantageously used as active ingredient in pharmaceutical compositions." (DTX 304 at 4:13-17.)

2003. A person of ordinary skill in the art would find this statement inherently and fatally ambiguous and would note the lack of any information in the patent supporting any of the various meanings that could be ascribed to this statement. (3/16/16 Matzger Tr. 72:15-17.)

2004. The alleged utility would not be accepted without question, and there is no data that supports the alleged utility. (*Id.* at 73:5-9; 82:20-24.) For these reasons the '364 patent specification fails to demonstrate utility. (*Id*. at 82:20-24).

2005. Dr. Matzger is a Professor of Chemistry at the University of Michigan. The Court accepted Dr. Matzger as an expert in organic materials in solid state and managed and prepared materials. (*Id.* at 66:23-67: 7; 68:7-14.) Dr. Matzger's testimony was credible and convincing.

2006. There is no definition of "ambient conditions" in the '364 Patent. (3/16/16 Matzger Tr. 73:17-24.) "Ambient conditions" is an ambiguous term; it could mean humidity and/or pressure and/or temperature. (*Id*.) The patent does not specify which of these various ambient conditions Form A is allegedly more stable under. (*Id.*)

2007. The '364 patent also does not define "stability." (*Id.* at 73:25-74:3; 3/11/16 Gruss Tr. at 82:25-83:8.) Without further information, one skilled in the art is not able to determine even which of different types of stability the applicant asserted that Form A had over Form B. (3/16/16 Matzger

Tr. 76:25-77:6.)

2008. "Stability" could denote from hydration stability, which concerns the propensity of a polymorph to incorporate water or solvent atoms within its lattice. (*Id.* at 74:5-18.) This is an issue in pharmaceuticals as it can change the bioavailability and manufacturing of a drug. (*Id.*)

2009. Alternatively, "stability" could also refer to chemical stability. (*Id*. at 74:23-75:8; 3/11/16 Gruss Tr. 87:15-22.) Chemical stability is the propensity to degrade into other molecules. (3/16/16 Matzger Tr. at 74:23-75:8.) This is linked to shelf-life because if an active pharmaceutical ingredient is degrading it may lose its appropriate medicinal action. (*Id.*)

2010. Alternatively, "stability" could refer to thermodynamic stability. (*Id.* at 75:13-21.) Thermodynamic stability relates to the solid-solid conversion between crystal structures at a given temperature. (*Id.*) Thermodynamic stability is linked to solubility in the body, which can impact bioavailability and be important for pharmaceuticals. (*Id.* at 75:24-76:4.)

2011. Plaintiffs' expert, Dr. Bernstein agreed that "stability" is a vague term and can mean at least either chemical stability or polymorphic stability. (3/22/16 Bernstein Tr. 15:11-17).

2012. There is no data in the patent specification demonstrating that Form A is more stable than the alleged prior art Form B using any of the various separate meanings of stability. (3/16/16 Matzger Tr. at 74:19-20; 75:9-10; 77:7-10.)

2013. Absent data supporting that Form A is in fact more stable with respect to a particular type of "stability," a POSA would not accept without question a conclusory statement that Form A is allegedly more stable because polymorph properties are unpredictable. (3/16/16 Steed Tr. at 45:17-19; 3/21/16 Bernstein Tr. 197:25-198:8; 3/22/16 Bernstein Tr. 36:16-37:2.)

B. Thermodynamic Stability Still Has No Demonstrated Utility

2014. The selection of a polymorph is much more complicated than simply saying that the thermodynamically stable form is always the desired form. (3/22/16 Bernstein Tr. 34:21-25; PTX

680 at JN_NUCYNTA_0063961.)

2015. Greater thermodynamic stability does not, without more, demonstrate utility because that property is often disfavored for pharmaceutical formulations. (3/16/16 Matzger Tr. at 76:5-15; 77:21-25; 3/22/16 Bernstein Tr. 34:12-13; 35:1-13; DTX 2001 at ¶¶ 5, 23; PTX 681 at JN_NUCYNTA_0063991; PTX 691 at JN_NUCYNTA_0064128.) In many cases, a less thermodynamically stable form is favorable because it will lead to better solubility and better bioavailability. (*Id.*) "It is crucial that a crystal form be sufficiently soluble and bioavailable in order to be useful as a pharmaceutical product." (3/22/16 Bernstein Tr. 33:20-34:2; 37:7-10.)

2016. Dr. Bernstein agreed that a crystal form must be sufficiently soluble and bioavailable in order to be useful as a pharmaceutical product, explaining "it's got to be bioavailable . . . sometimes you get fantastic stability and it doesn't have any therapeutic value. It goes in one end and comes out the other." (*Id.* at 16:10-14.)

2017. Dr. Gruss testified that good solubility (associated with good bioavailability) usually correlates with relatively low thermodynamic stability. (3/11/16 Gruss Tr. 85:24-86:18.)

2018. There are several examples of the more thermodynamically stable form of a polymorph being unsuitable for pharmaceutical formulations because of the poor solubility, such as ritonavir and chloramphenicol palmitate. (3/22/16 Bernstein Tr. 35:14-36:15; 3/21/16 Bernstein Tr. at 207:20-208:4; 230:16-24; PTX 681 at JN_NUCYNTA_0063987.)

2019. There is no way to predict whether the most stable form of a crystal will be sufficiently soluble, bioavailable or processable to perform adequately in a pharmaceutical product. (*Id.* at 34:2-20.) As Dr. Bernstein testified, to make such a determination "one has to do the experiment, do bioavailability and solubility tests." (*Id.* at 34:7-13.) To know if thermodynamic stability of tapentadol is useful, a POSA would need to see bioavailability and/or solubility data.

(3/16/16 Matzger Tr. at 76:5-15; 77:21-25; 78:1-19; PTX 681 at JN_NUCYNTA_0063990.)

2020. There is ***no*** solubility or bioavailability data in the '364 patent specification with respect to Form A or Form B. (3/16/16 Matzger Tr. at 78:13; 3/10/16 Buschmann Tr. 166:24-167:2; DTX 304.)

2021. Internal data at Grünenthal shows that there is no material difference between Form A and Form B with regard to usefulness as a pharmaceutical product. (3/22/16 Bernstein Tr. at 16:15-18; DTX 1158 at 14; DTX 1060; DTX 928; 3/11/16 Gruss Tr. 90:9-24, 94:17-22.) This data is not disclosed in the '364 Patent. (3/11/16 Gruss Tr. 90:25-91:12; DTX 304.)

2022. The evidence demonstrated that the concept of greater thermodynamically stability does not constitute a quality of utility in this case, given the total lack of information in the patent specification on the qualities of Form A as a pharmaceutical product. (FOF ¶¶2014 -2022.)

C. There Is Insufficient Data to Determine the Thermodynamic Stability of Form A at Any Temperature That Matters for a Pharmaceutical Product

2023. Relative thermodynamic stability of polymorphs is usually determined by solubility data. (3/10/16 Buschmann Tr. 167:3-5; 3/16/16 Matzger Tr. at 78:3-10.) Scientists in the field deem relatively solubility data as the main indicator of thermodynamic stability. (DTX 205 at 3; DTX 141.)

2024. The '364 Patent specification does not contain any solubility data (or any other data showing relative thermodynamic stability) at ambient conditions. *See* FOF 2020.

2025. Dr. Bernstein relied exclusively on Example 16 for alleged data to support the patent's assertions of utility. (3/21/16 Bernstein Tr. 196:4-197:1.) But, Example 16 is a variable temperature XRPD experiment run where "Form A converted to Form B from 40-50°C [i.e. 104 -122 °F] during the experiment" and "the result is reversible with Form B changing over into Form A at lower temperature." (DTX 304 at 18:52-56.) But that experiment does not provide relative solubility (how thermodynamic stability is determined) and the lower temperature at which Form B changes

over into Form A is not specified. (3/16/16 Matzger Tr. at 79:6-8). A person of skill in the art reading the patent would only have claim 17 to attempt to determine that information. (*Id.* at 79:14-80:4) Claim 17, in turn, states that Form B is converted to Form A when cooled between -4 and -80 °C, which is 24.8 F to -112 °F. (DTX 304 at 20:18-23).

2026. Thus, a POSA reading the patent does not know the thermodynamic stability of Form A at any temperature that matters for a pharmaceutical product: e.g., at either room temperature (22 °C/72 °F) (the temperature likely for manufacture) or body temperature (37 °C/98.6 °F) (the temperature of ingestion/digestion), which are the only two potentially pertinent temperatures for pharmaceutical products. (3/16/16 Matzger Tr. at 80:5-81:8). A POSA would not regard Example 16 as supporting the asserted utility, as Example 16 is not "data" and particularly not data at room temperature. (*Id.* at 78:22- 81:8).

2027. Defendants have proven that the '364 patent specification lacks utility because the statement of utility is inherently vague and insufficient; and even assuming that the specification's statement were clear, a POSA reading the specification would not find that there was sufficient disclosure to support that asserted utility.

V. UNCLEAN HANDS

2028. The '364 Patent represented that Grünenthal had "surprisingly found" "a new form (Form A) of [tapentadol] hydrochloride which is different from the form already known (Form B) obtained by the procedure described in example 25 of U.S. Pat. No. 6,248,737 and U.S. Pat. No. 6,344,558 as well as EP 693 475 Bl." (DTX 304 at 1:58-63.) Grünenthal told the PTO that Form A was patentable because it was distinct from the so-called "Form B" that allegedly is the product of Example 25 of Plaintiffs' own prior art '737 patent. (*Id.* at 1:58-63; DTX 87 at 9.)

2029. The PTO Examiner expressly relied on Grünenthal's representations in deciding to grant the '364 Patent and made the following statement in his "Reasons for Allowance":

> The crystalline form recited in the instant claims and supported by the instant Figures and throughout the specification is novel and nonobvious over the closest prior art disclosed in United States Patent No. 6,248,737. In the instant case, Applicant's compared the form of the closest prior art with the new crystalline form. As claimed, the new crystalline form is novel and nonobvious over the prior art form in view of the evidence provided in the instant specification.

(DTX 1361 at JN_NUCYNTA_0059017.)

2030. Example 7 of the '364 Patent is named "Preparation of Form B(1)," and describes the preparation of "Form B(1)" of tapentadol hydrochloride "prepared according to example 25 of European Patent EP 693 475 B1." (DTX 304 at 7:30-41.) Example 7 states the crystalline Form B of tapentadol "was generated as proven by X-ray powder diffraction." (*Id.*)

2031. Example 10 of the '364 patent is entitled "X-Ray Powder Diffraction [XRPD] Patterns of Forms A (1) and B (1)." and states "[t]he X-ray pattern for Form A is shown in FIG. 1, the X-ray pattern for Form B in FIG. 4." (*Id.* at Ex. 10; 8:3-17.)

2032. Figure 4 of the '364 patent is entitled "Fig. 4: XRPD pattern of Form B." Figure 8 of the '364 patent purports to be the labeled XRPD pattern in Figure 4. (*Id.* at Figs. 4, 8.) These patterns are the only Form B patterns in the '364 patent. (*Id.*; 3/16/16 Matzger Tr. 89:12-18.)

2033. The XRPD patterns of Figures 4 and 8 of the '364 patent were taken from a sample of batch CEPM1a, which was **not** prepared according to the procedure disclosed in Example 25 of the '737 patent. (DTX 146 at 11, 14 and 22; DTX 39 at 49; ECF No. 160-29 (14-3941-Plaintiffs' SOF # 34; ECF No. 160-28 at 5.) CEPM1a was made from an unusual process, in which the impure part of a previously-filtered solution was concentrated to make a solid. (3/16/16 Matzger Tr. 90:17-92:9; DTX 1097.) CEPM1a also showed the presence of Form A. (DTX 1093.) None of this information was disclosed to the Patent Office. (3/16/16 Matzger Tr. 89:20-21; 92:21.) Thus, the '364 patent contains no data whatsoever that corresponds to Form B obtained by following Example 25 of the prior art. (*Id.* 89:12-21.) Indeed, Dr. Bernstein did not even contend otherwise. *See* e.g.

(3/21/16, 3/22/16 Bernstein Tr.)

2034. When Grünenthal employee Marita Mueller was asked to attempt to perform Example 25 for the first time, she was told to write in her lab notebook that the result was Form B before the sample results had even come back. (Mueller Depo Tr. at 85:25-87:8.) This was before Grünenthal had grounds to believe that Form B was the result of Example 25, since this was the first re-creation of Example 25 performed by Grünenthal. *See e.g. id.*

2035. Form A was the ubiquitous form present in the samples of tapentadol hydrochloride synthesized at Grünenthal. (DTX 1060; DTX 1088 at 3; DTX 1087 at 16, DTX 1075 at 1; DTX 1242 at p. 13; 3/16/16 Matzger Tr. 84:24-88:21.)[3] Grünenthal and SSCI had difficulty even making a relatively stable Form B. (*Id.*) In order to even obtain a relatively stable Form B polymorph at room temperature, Grünenthal had to incorporate impurities or engage in milling. (DTX 1075 at 4; 3/16/16 Steed Tr. 25:16-21; 3/16/16 Matzger Tr. 109:24-110:3: DTX 1001 at 9, 10).

2036. Despite Grünenthal's internal knowledge of these facts, they disclosed none of it to the PTO and instead wrongly characterized Form A as the "new form." (DTX 304 at 1:58-63).

2037. Various examples in the '364 Patent are methods of preparing Form A starting with Form B of tapentadol hydrochloride prepared according to Example 25 but were never actually performed as written in the specification. *See e.g.* (DTX 304 at Examples. 2-3, 5; Matzger Tr. 93:1-94:23; 137:2-139:6.)

2038. First for instance, Example 2, titled a Method of Preparation of Form A, states the starting materials was prepared according to Example 25 of the European patent, which Plaintiffs represent gives rise to Form B. (DTX 304 at 5:35-51; 3/16/16 Matzger Tr. 93:10-18.) Plaintiffs' corporate designee identified the basis for Example 2 as the SSCI experiments. (DTX 39 at 45.) In

[3] CG5503 is an internal Grünenthal names for tapentadol hydrochloride. (DTX 87 at 9.)

the SSCI document, the experiment of Example 2 is found, but the SSCI document clearly states that the starting sample as received from Grünenthal was Form A. (DTX 1001 at 5, 13.)

2039. Dr. Bernstein does not deny that examples (such as Example 2) started with Form A, he simply maintained that it "doesn't matter." (3/21/16 Bernstein Tr. 293:14-19; 300:2-6.)

2040. Several examples, such as Example 2, conclude by saying that the form allegedly produced "was proven by X-ray powder diffraction and by RAMAN microscopic analysis." (DTX 304 at 5:50-51.) This was not true, because SSCI did not conduct Raman microscopic analysis (a process which would have shown impurities), the only performed Raman spectroscopy. (3/16/16 Matzger Tr. 137:10 – 138:14, 159:10-19). Dr. Bernstein did not dispute that RAMAN microscopic analysis was written in the patent but not actually performed.

2041. Grünenthal's deceptive intent can be inferred from the aforementioned direct and circumstantial evidence showing Grünenthal withheld material information from Patent Office. Grünenthal intentionally withheld material facts in order to mislead the Patent Office, making its patent application as a whole misleading. Grünenthal's concealment and nondisclosure is evidence of a false representation, because the concealment of information regarding Form A was a representation that what it had disclosed to the PTO was the whole truth.

2042. These unconscionable act had immediate and necessary relation to the equity that Plaintiffs now seek. As such for the reasons listed above, Grünenthal has come to this Court with unclean hands, which renders the '364 patent unenforceable.

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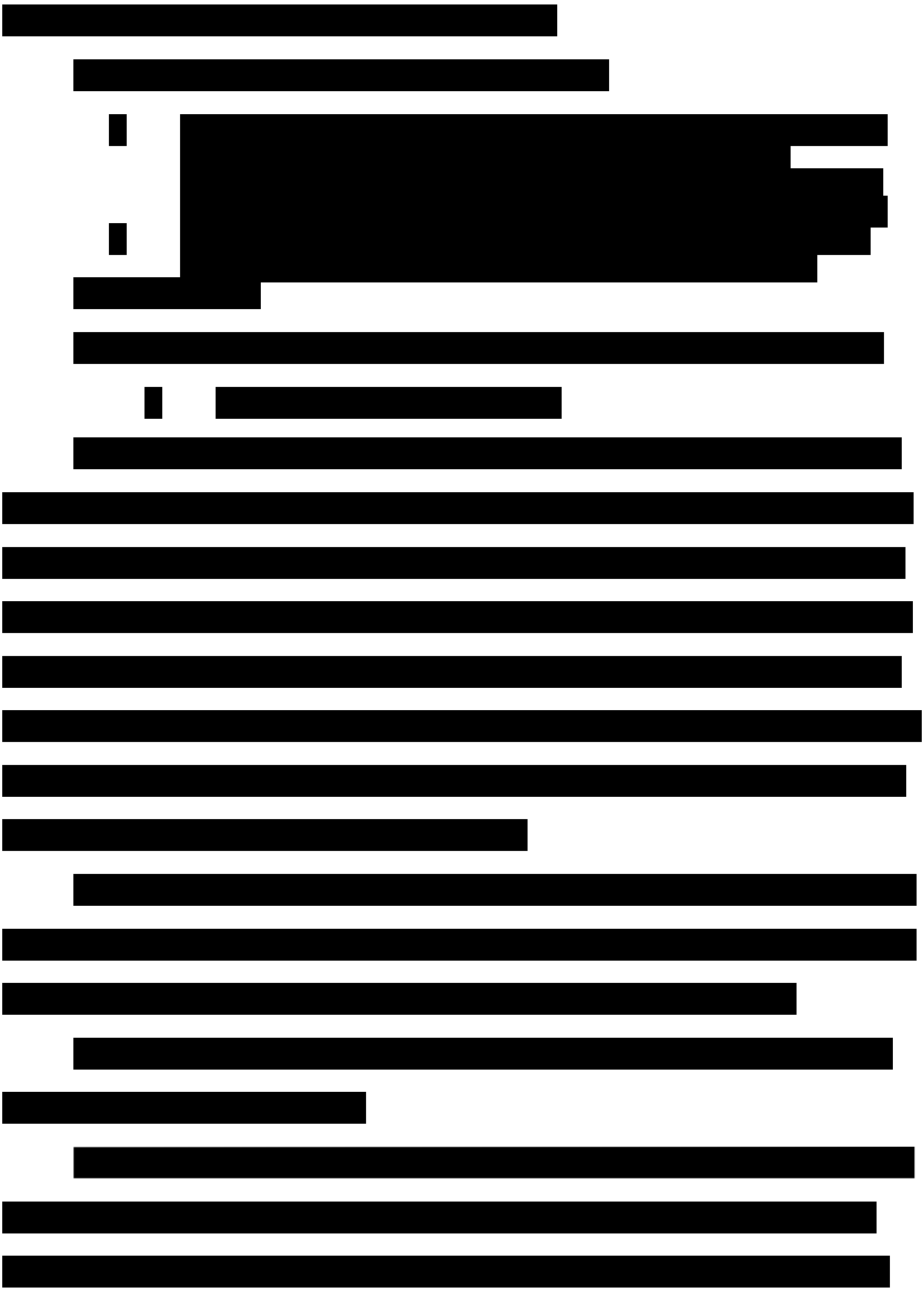

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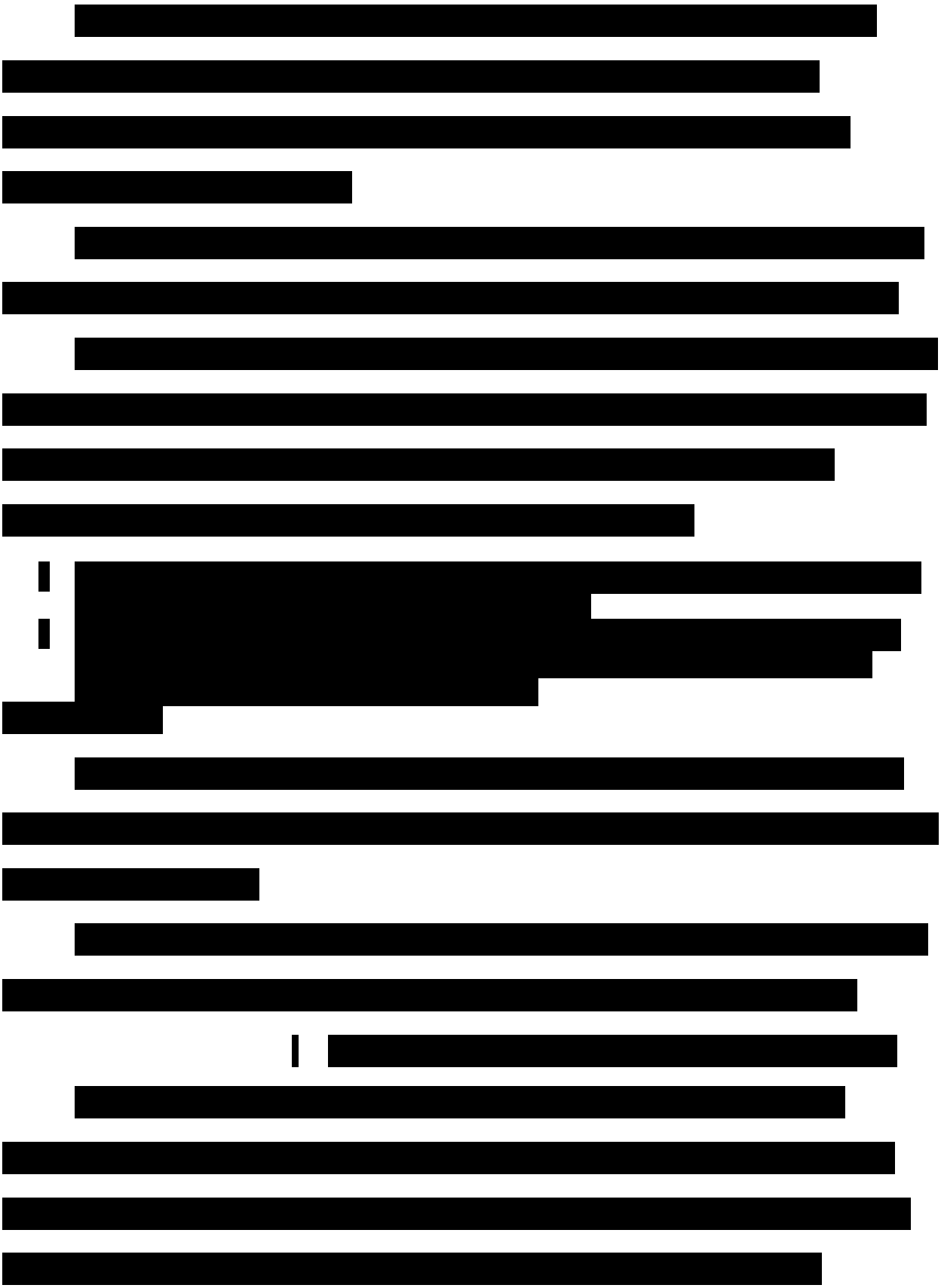

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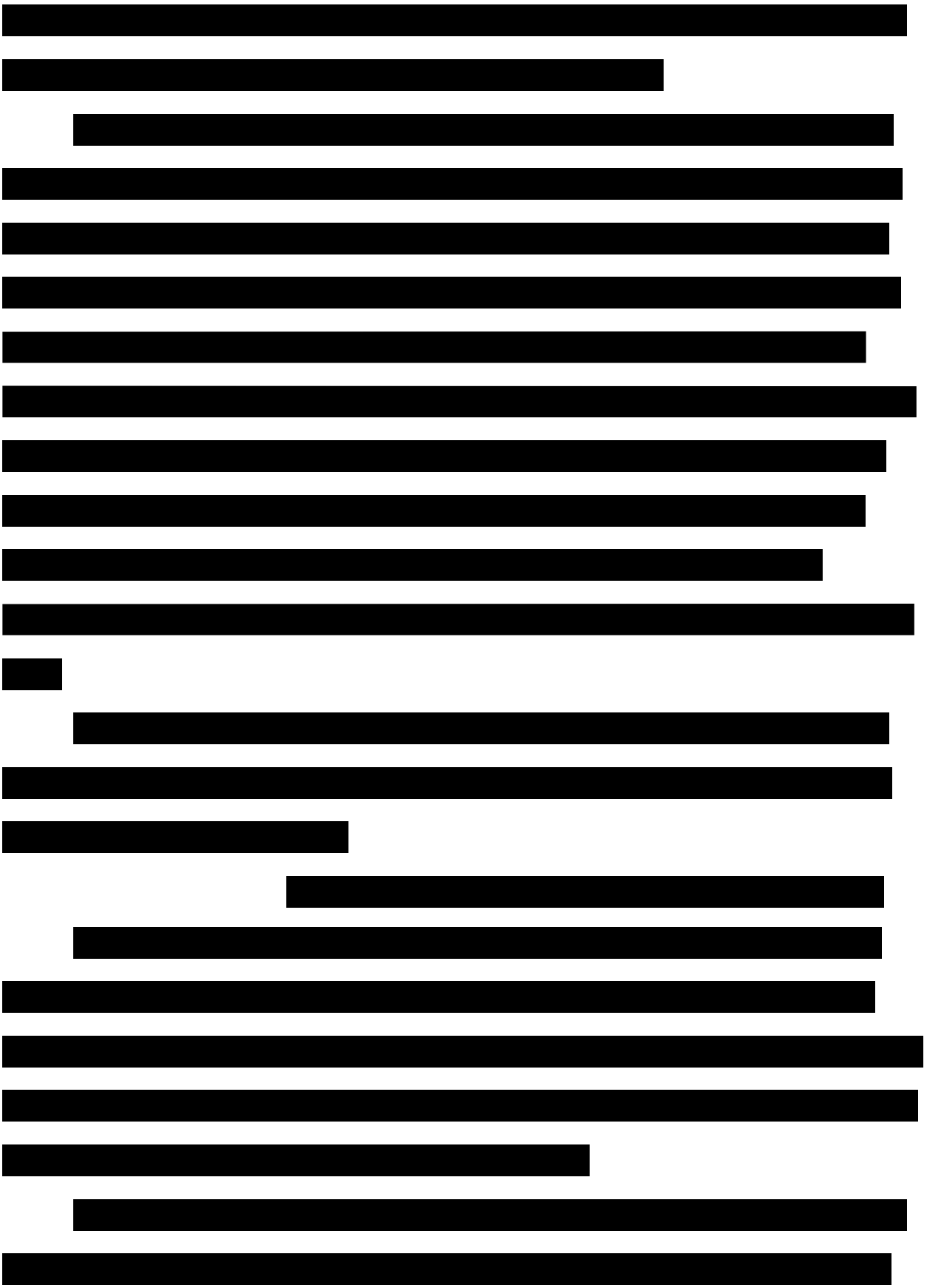

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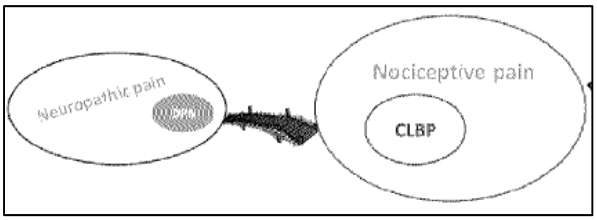

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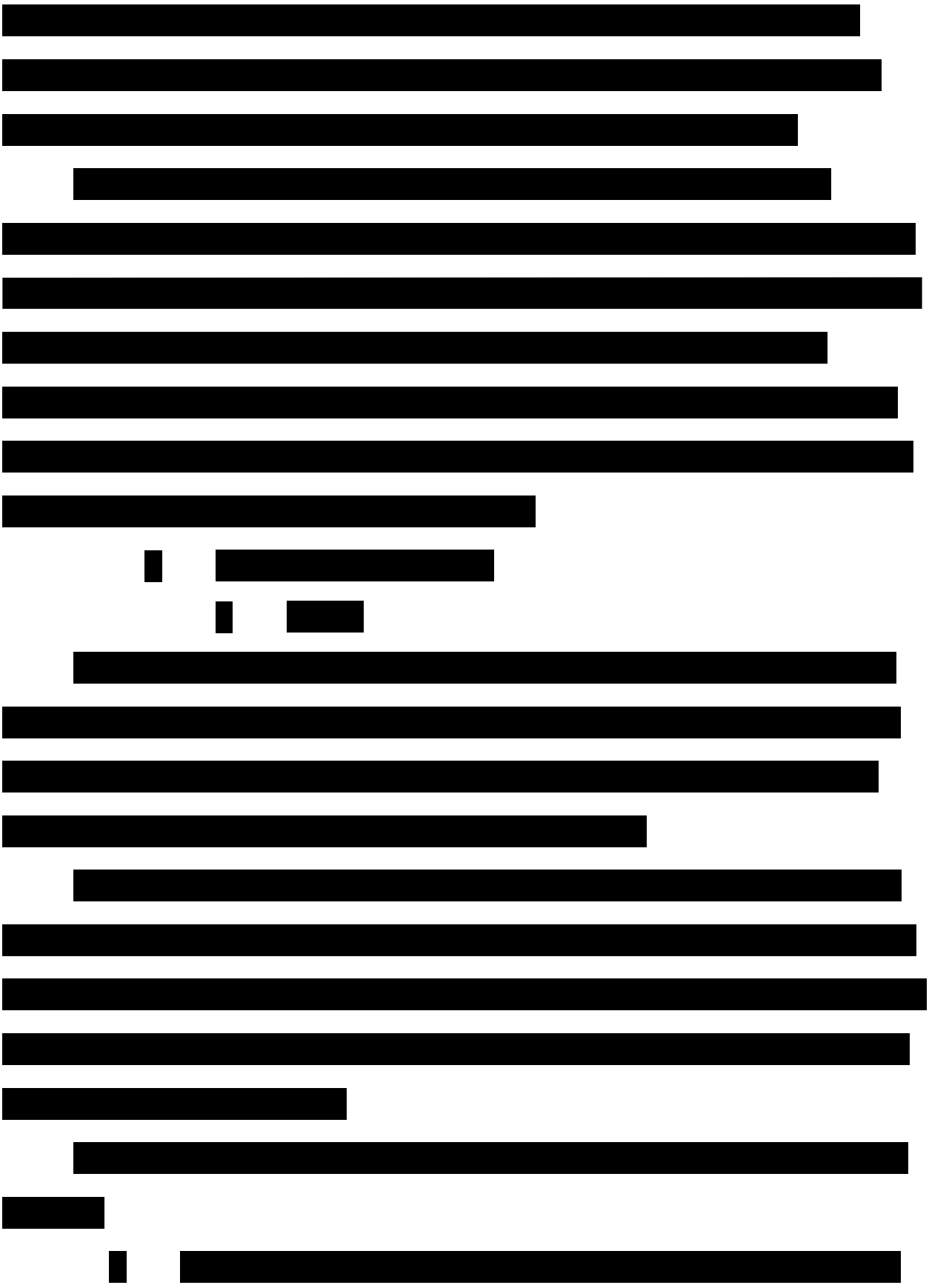

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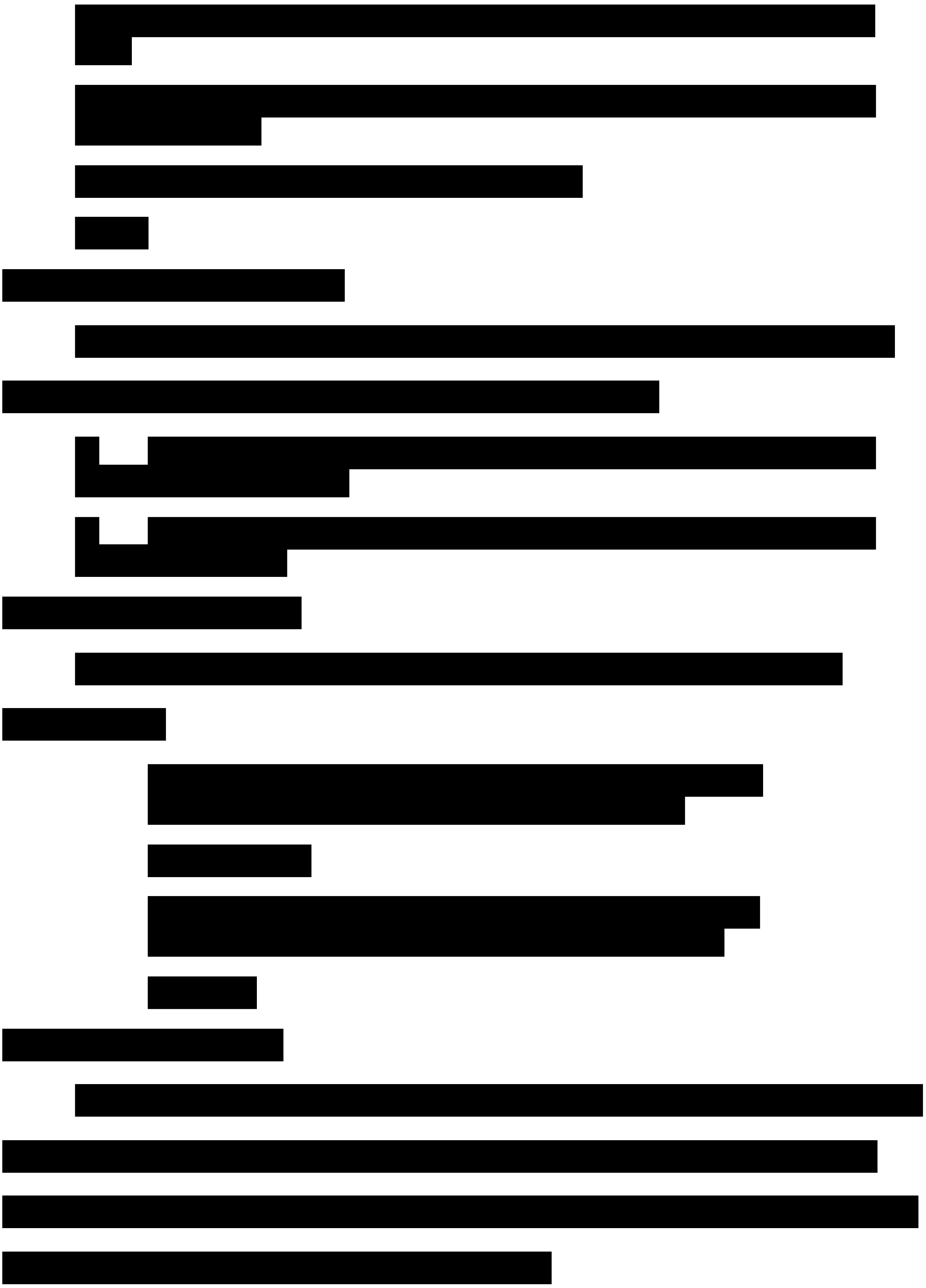

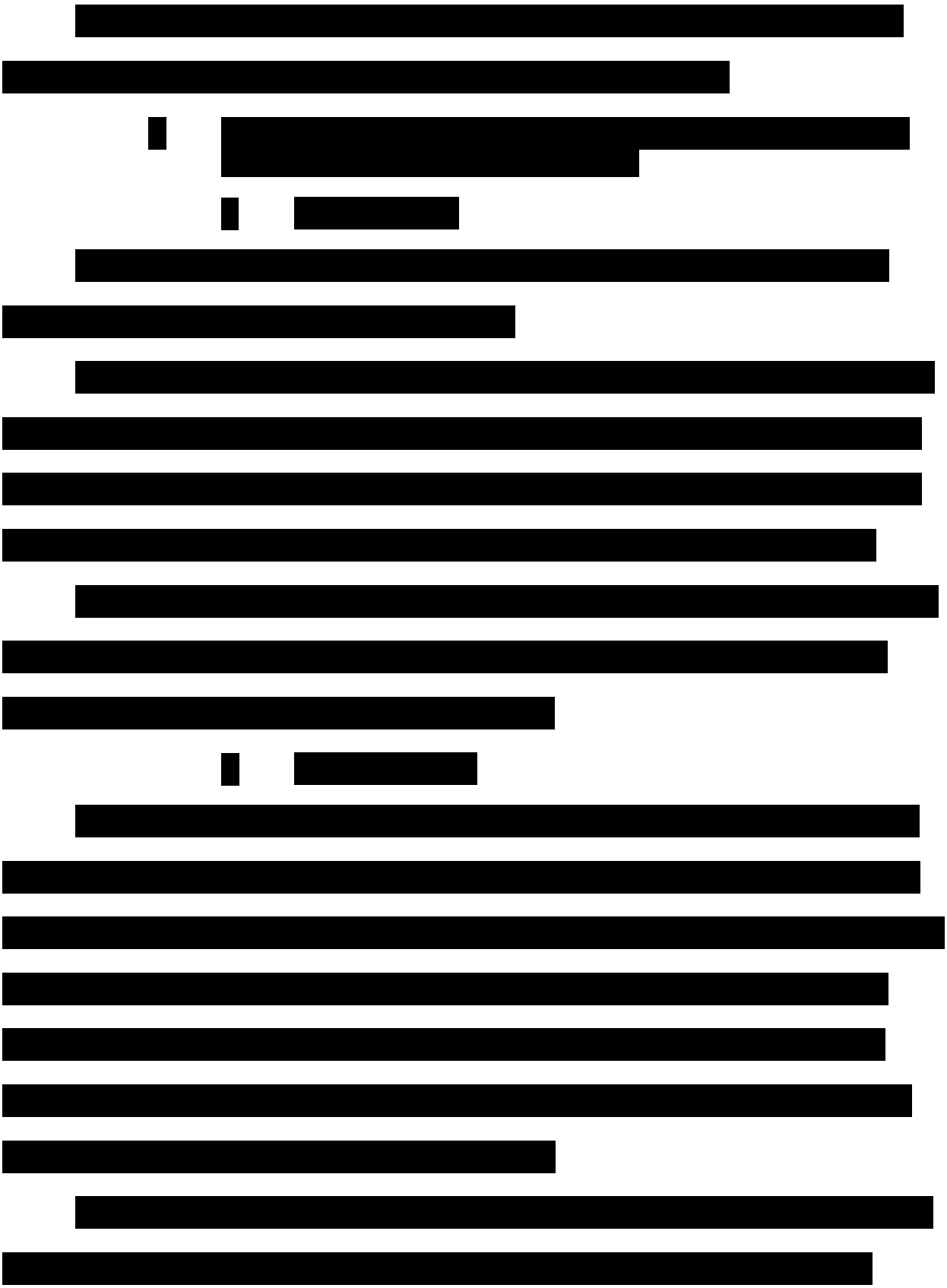

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VIII. THE CLAIMS OF THE '130 PATENT ARE INVALID

A. The Claims of the '130 Patent Are Anticipated by the '737 Patent

3501. U.S. Patent No. 6,248,737 ("the '737 patent") issued on June 19, 2001, more than one year before the March 2007 filing of the earliest application to which the claims of the '130 patent may claim priority. DTX-752 at Front Page; 3/21/16 Buvanendran Tr., 78:3-7.

3502. Example 25 of the '737 patent discloses tapentadol hydrochloride, and describes it and related compounds as being "suitable for the treatment of severe pain." DTX-752 at Example 25 and 1:52-55; 3/21/16 Buvanendran Tr., 78:8-79:2.

3503. The '737 patent describes a method of administering tapentadol hydrochloride to a subject, just as in the claims of the '130 patent. 1/23/16 Brown Tr. 53:17-23; 56:1-14.

3504. The population with severe pain will necessarily include a subpopulation with polyneuropathic pain. 3/21/16 Buvanendran Tr., 79:21-80:6.

3505. Dr. Brown admitted that severe pain can include polyneuropathic pain. 3/23/16 Brown Tr. 48:22-29:1.

3506. Dr. Brown acknowledged that polyneuropathic pain has always been a form of severe pain.

> Q. Polyneuropathic pain has always been a form of severe pain; correct?
>
> A. In the grand scheme of the world, probably back to when people walked upright, yes.

3/23/16 Brown Tr. 49:3-6.

3507. Dr. Brown admitted that some of the population of patients with severe pain would have polyneuropathic pain. 3/23/16 Brown Tr. 49:13-17.

3508. Dr. Brown impermissibly limited the meaning of "severe pain" in the '737 patent to severe nociceptive pain because in her opinion the mouse study of the example in the '737 patent is a model of nociceptive pain. 3.23.16 Brown Tr. 11:24-12:24.

3509. The ’737 patent explicitly states that its teachings are not to be limited by the examples. DTX-752 at col. 23, ll. 41-43 (“The foregoing description and examples have been set forth merely to illustrate the invention and are not intended to be limiting.”).

B. The Claims of the ’130 Patent Are Invalid for Obviousness-Type Double Patenting

4001. Plaintiffs asserted claims 1 and 2 of the ‘130 patent against defendants Actavis, and Roxane. Buvanendran 3/21/16 Tr. 48:4-7; Brown 3/14/16 Tr. 42:4-6. Plaintiffs asserted claims 1, 2, 3, and 6 of the ’130 patent against defendant Alkem. Buvanendran 3/21/16 Tr. 48:4-10; Brown 3/14/16 Tr. 42:1-3; Brown 3/15/16 Tr. 82:9-12; DTX 00075_00018, 18:2-21.

4002. There is no meaningful difference between the term “diabetic polyneuropathic pain” in claim 3 and “diabetic polyneuropathy” in claim 6 of the ’130 patent. DTX 00075_0010, 8:17-21; Buvanendran 3/21/16 Tr. 55:9-14; *id.* 55:23-56:1; Brown 3/14/16 Tr. 43:3-5.

1. ’593 is an earlier issued patent and commonly owned with the ’130 patent

4003. The ’593 patent was reissued on April 24, 2007. DTX 01346_0002. The ’130 patent was issued on September 17, 2013. DTX 00075_0001. Thus the claims of the ’593 patent were earlier issued than the claims of the ’130 patent.

4004. According to the Orange Book, the claims of the ’130 patent expire September 22, 2028. According to the Orange Book, the claims of the ’593 patent expire August 5, 2022. The ’130 patent extends the patent exclusivity for Plaintiffs by more than six years for the use of tapentadol hydrochloride to treat polyneuropathic pain.

4005. Both the ’593 patent and the ’130 patent are commonly owned by the same entity, Grünenthal. DTX 01346_0002; DTX 00075_0001; Buvanendran 3/21/16 Tr. 50:11-20. The ’593 patent is assigned on its face to Grünenthal. DTX 01346_0002; Buvanendran 3/21/16 Tr. 50:11-

14. The ’130 patent is also assigned on its face to Grünenthal. DTX 00075_0001; Buvanendran 3/21/16 Tr. 50:11-16.

2. Claim 1 of the ‘130 patent is not patentably distinct from claim 117 of the ’593 patent

4006. Dr. Buvanendran compared claim 117 of the ’593 patent to the claims of the ’130 patent to analyze the issue of double patenting. Buvanendran 3/21/16 Tr. 51:5-18.

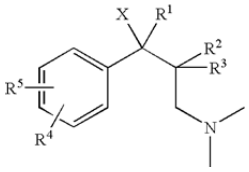
1. Claim 117 of the ’593 patent reads:

> 117. A method according to claim 8, wherein the compound is (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (-21).

DTX 01346_00022, 38:8-10.

4007. The method of Claim 8, from which claim 117 depends, provides:

> 8. A method of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of a 1-phenyl-3-dimethyl-aminopropane compound corresponding to formula I



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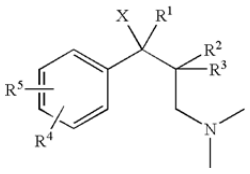
DTX 01346_00015-16, 24:54-25:34.

4008. Thus if claim 117 of the ’593 patent is rewritten in independent form by incorporating the “method of claim 8” into the text of claim 117, then claim 117 can be written as follows:

> 117. A method [of treating a mammal suffering from pain, said method comprising administering to said mammal an effective analgesic amount of a 1-phenyl-3-dimethyl-aminopropane compound corresponding to formula I



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wherein the compound is (-)-(1R,2R)-3-(3-dimethylamino-1-ethyl-2-methylpropyl)-phenol hydrochloride (-21).

3. **One relevant difference exists between claim 117 of the '593 patent and the asserted claims**

4009. When directly compared, there are two difference between claim 117 of the '593 patent and claim 1 of the '130 patent. DTX 01346_0022, 38:7-9 (dependent claim 117); *id.* at 0015, 24:54-25:34 (independent claim 8); DTX 00075_0001; Buvanendran 3/21/16 Tr. 50:11-20; *id.* 51:14-52:12.

4010. The first difference, is that claim 117 of the '593 patent refers to treating "mammal" while claim 1 of the '130 patent refers to treating a "subject." There is no dispute that this difference does not render claim 1 of the '130 patent patentably distinct from claim 117 of the '593 patent. Buvanendran 3/21/16 Tr. 51:19-52:1. The second difference, is that claim 117 of the '593 patent refers to treating "pain" while claim 1 of the '130 patent refers to treating "polyneuropathic pain." The parties dispute whether this difference renders claim 1 of the '130 patent patentably distinct from claim 117 of the '593 patent. Buvanendran 3/21/16 Tr. 52:2-12.

4. **A POSA would consider "pain" to be an umbrella term including both nociceptive and neuropathic pain**

4011. The term "pain" in claim 117 of the '593 patent is an umbrella term that refers to "the mechanisms or pathophysiology of pain, where the pain is originating from." Buvanendran 3/21/16 Tr. 52:16-21; Brown 3/15/16 Tr. 18:3:3-7. As such, the term "pain" in claim 117 of the '593 patent "included the concepts of nociceptive pain and neuropathic pain." Buvanendran 3/21/16 Tr. 52:13-24; *id.* 54:2-4.

4012. Each of the mechanisms of pain can be further divided by considering the location of pain. Neuropathic pain can be divided into either mononeuropathic pain or polyneuropathic pain, depending on whether the pain is associated with one nerve or multiple nerves. Buvanendran 3/21/16 Tr. 53:13-19; Brown 3/15/16 Tr. 18:8-14. Nociceptive pain can be divided depending on whether the pain originates in an extremity (somatic) or inside the abdomen or intraabdominal cavity (visceral). Buvanendran 3/21/16 Tr. 53:20-24; *id.* 54:2-4.

4013. The understanding of the term "pain" to a person of ordinary skill in the art ("POSA") is the same whether considered from 1994, the priority date of the '593 patent, or from 2007, the priority date of the '130 patent. Buvanendran 3/21/16 Tr. 52:13-24; 53:6-10. A POSA would consider "pain" to refer to both nociceptive and neuropathic pain. Buvanendran 3/21/16 Tr. 52:13-24; *id.* 54:2-4, 17-24; *id.* 59:4-11; Brown 3/15/16 Tr. 73:8-11.

4014. The broad reading of the term "pain" is supported by the specification of the '593 patent. Under the heading "Summary of the Invention," the inventors described the "underlying object of the present invention" as creating compounds "which are suitable for the treating of ***severe pain***." DTX 01346_4, 1:60-63 (emphasis added); Buvanendran 3/21/16 Tr. 54:4-8; *see* Brown 3/15/16 Tr. 75:14-76:4. Dr. Brown testified that the mention of "severe pain" in Defendants' proposed labels on its own is a specific instruction to use tapentadol for polyneuropathic pain. Brown 3/14/16 Tr. 103:11-104:9; Brown 3/15/16 Tr. 72:24-73:4; *see also* Brown 3/23/16 AM Tr. 48:20-49:6; *id.* 49:13-17; Brown 3/14/16 Tr. 41:14-23; *id.* 51:10-22.

4015. Relevant literature from before the filing of the '593 patent confirms that the term "pain" referred to both nociceptive and neuropathic pain. The reference *Issues in Pain Management* includes a chapter authored by Dr. Donna L. Hammond, entitled "Inference of Pain and Its Modulation from Simple Behaviors" ("the Hammond reference"), published in 1989.

DTX 01576_0003; Buvanendran 3/21/16 Tr. 57:16-19. In the reference, Dr. Hammond discusses the nomenclature used to discuss pain. DTX 01576_0004; Buvanendran 3/21/16 Tr. 58:7-10.

4016. In discussing the different types of pain, Dr. Hammond refers both to nociceptive pain and hyperalgesia. DTX 01576_0004. The description of hyperalgesia provided by Dr. Hammond is "increased sensitivity and reactivity to a noxious stimulus." DTX 01576_0004. This understanding is consistent with the definition provided by Drs. Buvanendran and Christoph. Buvanendran 3/21/16 Tr. 58:23-59:3; Christoph 3/14/16 AM Tr. 31:5-6.

4017. Hyperalgesia is a symptom of only nociceptive pain, not nociceptive pain. Buvanendran 3/21/16 Tr. 59:4-6. Dr. Christoph consistently used the term hyperalgesia to describe neuropathic pain in his animal models. *E.g.*, Christoph 3/14/16 AM Tr. 33:24-34:8 ("you see a dose-dependent inhibition of mechanical hyperalgesia, or polyneuropathic pain"); *id.* 41:15-43:8; *id.* 49:3-7; *id.* 49:25-50:3; *id.* 50:16-18.

5. If "pain" is an umbrella term, then the asserted claims of the '130 patent are invalid.

4018. Because term "pain" refers to both nociceptive and neuropathic pain, claim 117 of the '593 patent encompasses all of the subject matter of the asserted claims 1 and 2 of the '130 patent. Buvanendran 3/21/16 Tr. 54:17-55:8; *id.* 56:16-20; Brown 3/15/16 Tr. 18:3:3-7. The later issued claims 1 and 2 of the '130 patent are directed to a particular use described in the earlier issued '593 patent of the claimed compositions. DTX 01346_0004, 1:60-63; Buvanendran 3/21/16 Tr. 54:4-55:8; *id.* 56:16-20.

4019. A POSA in 1994 would understand the term "pain" to refer to a genus of few species. Particularly, a POSA would immediately envisage the two mechanisms of pain—neuropathic and nociceptive—and the two locations of pain within each mechanism, thus

totaling four species of "pain": mononeuropathic, polyneuropathic, somatic, and visceral. Buvanendran 3/21/16 Tr. 52:13-24; *id.* 54:2-4; Brown 3/15/16 Tr. 73:8-15.

4020. Claims 3 and 6 of the '130 patent, referring to "diabetic polyneuropathic pain" and "diabetic polyneuropathy," are encompassed by claim 117 of the '593 patent. Buvanendran 3/21/16 Tr. 56:2-6. Diabetic polyneuropathic pain is one of the most common reasons for polyneuropathic pain in patients seeking medical treatment. Buvanendran 3/21/16 Tr. 56:7-12; Brown 3/15/16 Tr. 72:24-73:7.

4021. The use of tapentadol to treat diabetic polyneuropathic pain is disclosed as a utility for the compound in the specification of the '593 patent. DTX 01346_0004, 1:60-63; Buvanendran 3/21/16 Tr. 54:4-8. The later issued claims 3 and 6 of the '130 patent are directed to a particular use described in the earlier issued patent of the claimed compositions. DTX 01346_0004, 1:60-63; Buvanendran 3/21/16 Tr. 54:4-8; *id.* 56:2-12.

6. Even if "pain" means nociceptive pain only, the asserted claims of the '130 would have been obvious to a person of ordinary skill in the art

4022. Even if "pain" in claim 117 of the '593 patent refers only to nociceptive pain, a POSA reading that claim in March 2007 would have found it obvious to use the compound tapentadol to treat polyneuropathic pain. Buvanendran 3/21/16 Tr. 59:17-23. The time point of March 2007 is relevant because that is the filing date of the '130 patent. DTX 00075_0001; Buvanendran 3/21/16 Tr. 10-12.

4023. Claim 117 of the '593 patent discloses the compound tapentadol. DTX 01346_0022, 38:8-10. In addition to the chemical name, claim 117 also refers to the compound numbered (-21). *Id.* Compound (-21) is identified in the specification of the '593 patent as the product of Example 25. *Id.* 19:12-30. Example 25 includes the structural drawing and chemical

name of tapentadol. *Id.* This information would allow a POSA in March 2007 to conclude that the compound is an opioid derivative.

4024. By March 2007, there was substantial literature establishing that opioids were effective for the treatment of polyneuropathic pain. Buvanendran 3/21/16 Tr. 59:24-60:9; Christoph 3/14/16 AM Tr. 103:15-23.

4025. The strong body of public literature establishing the effectiveness of opioids to treat neuropathic pain was recognized internally by Grünenthal. Buvanendran 3/21/16 Tr. 66:11-21. The conclusion reached by the inventors of the '130 patent in the internal reports is consistent with the conclusion reached by Dr. Buvanendran. Buvanendran 3/21/16 Tr. 59:21-23.

4026. Internal Report No. PH534, prepared by the inventors, is dated June 11, 2003. PTX 454 at 1, 3; DTX 01023_0001-02; Christoph 3/14/16 AM Tr. 32:4-34:4; *id.* 90:18-91:5. In the Discussion, the inventors of the '130 patent write: "Although there is a large consensus concerning the effectiveness of opioids in nociceptive pain, their efficacy in neuropathic pain was debatable until recent years (Portenoy, 1996; Dellemijn, 1999). However ***several studies have proven efficacy of opioids in neuropathic pain conditions*** (Dellmijn & Vanneste, 1997; Sindrup *et* al, 1999). PTX 454 at 14 (emphasis added). This statement is based on publicly available art published in the late 1990s—long before the filing date of the '130 patent. Christoph 3/14/16 AM Tr. 92:4-16.

4027. In report PH522, dated July 1, 2002, Dr. Christoph discussed the development of a consensus regarding the efficacy of opioids for the treatment of neuropathic pain: "Thus, the old dogma of lacking efficacy of opioids in the treatment of neuropathic pain holds no longer true." PTX 477 at GRT-NUC00054642; DTX 01030_0015; Christoph 3/14/16 AM Tr. 19-23.

This conclusion was based on the fact that "several studies have proven efficacy of opioids in neuropathic conditions." DTX 01030_0015.

4028. The article Harati et al., Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy, *Neurology*, Vol. 50: 1842-1846 (June 1998) was published more than one year before the filing date of the '130 patent. DTX 01605.

4029. The study described in the Harati reference was funded by the predecessor to Janssen, who originally marketed tramadol and tapentadol. DTX 01605_0002. The inventors of the '130 patent were aware of the Harati reference, and cited it in their internal reports regarding the development of tapentadol before the filing of the '130 patent. DTX 01030_0016; Christoph 3/14/16 AM Tr. 128:12-129:4; Christoph 3/14/16 PM Tr. 15:24-16:21. But the Harati reference was not disclosed by Grünenthal during the prosecution of the '130 patent, and was not considered by the examiner. *See* DTX 00075_0001 (Other Publications); *generally* PTX 01600.

4030. Tramadol was understood by persons of ordinary skill in the art in March 2007 to be an opioid derivative. Buvanendran 3/21/16 Tr. 61:12-17.

4031. The Harati publication describes a "multicenter, randomized, double-blind, placebo-controlled, parallel-group study of tramadol versus placebo" in patients suffering from diabetic peripheral neuropathy. DTX 01605_0002; *also id.* at 0003-6; Buvanendran 3/21/16 Tr. 60:24-61:17. The authors concluded that "patient assessments of pain intensity and pain relief showed that tramadol was significantly more effective than placebo for treating the pain of diabetic neuropathy." DTX 01605_0005. The authors also concluded that the tramadol trial described in the Harati publication "indicates that tramadol is an alternative to tricyclic drugs or anticonvulsants for treating the pain of diabetic neuropathy." *Id.* at 0006; *also id.* at 0002; Buvanendran 3/21/16 Tr. 61:7-11. Dr. Brown agreed that the Harati reference demonstrated

tramadol provided a benefit to patients with polyneuropathic pain. Brown 3/23/16 Tr. 94:20-95:1.

4032. The article Hollingshead, et al., Tramadol for Neuropathic Pain, *Cochrane Review*, (2006) was published and disclosed more than a year before the filing date of the '130 patent. DTX 00916. The Hollingshead article was not disclosed to the patent office and was not considered by the examiner during prosecution of the '130 patent. *See* DTX 00075_0001 (Other Publications); *generally* PTX 01600.

4033. The Hollingshead article is a Cochrane review that surveyed the available literature published between January 1980 and June 2005 regarding the efficacy of tramadol for treating neuropathic pain. DTX 00916_0001. The Cochrane review is well-regarded within the industry because of its highly selective grading system. Buvanendran 3/21/16 Tr. 62:1-10. The authors screened the data to only consider the well-controlled studies. DTX 00916_0002-03. Based on a review of the most reliable data, the authors concluded that "tramadol is an effective treatment for neuropathic pain." DTX 00916_0001, 0006-07; Buvanendran 3/21/16 Tr. 62:11-14.

4034. Dr. Brown's opinion that tramadol was not effective in treating neuropathic pain is based only on her personal experience, and not a review of the literature. Brown 3/23/16 Tr. 20:16-18.

4035. The article Gilron et al., Morphine, Gabapentin, or Their Combination for Neuropathic Pain, *New England Journal of Medicine*, Vol. 352:1324-34 (Mar. 31, 2005) was published more than one year before the filing date of the '130 patent. PTX 1141; Buvanendran 3/21/16 Tr. 62:16-18. The Gilron paper was not disclosed by Grünenthal and was not considered by the examiner during prosecution of the '130 patent. *See* DTX 00075_0001 (Other Publications); *generally* PTX 01600.

4036. The Gilron paper describes a randomized controlled trial comparing morphine alone, gabapentin alone, morphine in combination with gabapentin, and placebo in patients with diabetic peripheral neuropathy and post herpetic neuralgia. PTX 1141 at JN_NUCYNTA_1634614-16; Buvanendran 3/21/16 Tr. 62:16-1. Morphine is an opioid compound. Buvanendran 3/21/16 Tr. 62:24.

4037. The results of the well-controlled clinical trial "replicates evidence from previous studies of the efficacy of opioids in neuropathic pain." PTX 1141 at JN_NUCYNTA_1634622; Buvanendran 3/21/16 Tr. 63:5-10. In other words, the Gilron paper confirmed the findings of earlier studies showing the efficacy of opioids in the treatment of neuropathic pain. *Id.*

4038. The Gilron paper also shows that when compared to placebo, morphine alone works better than gabapentin alone for the treatment of neuropathic pain. PTX 1141 at JN_NUCYNTA_1634622-23; Fig. 2 (lower pain scores indicate better results). The Gilron paper would be considered strong evidence because it is published in the *New England Journal of Medicine*, the journal with one of the highest impact factors within the medical community. Buvanendran 3/21/16 Tr. 63:1-4.

4039. Treatment recommendations, or algorithms, by experts in the industry recognized the efficacy of opioids in the treatment of neuropathic pain. Treatment algorithms provide a step-wise process for physicians to choose appropriate medications for patients. Buvanendran 3/21/16 Tr. 63:13-24.

4040. The paper Namaka et al., A Treatment Algorithm for Neuropathic Pain, *Clincial Therapeutics*, Vol 26, No. 7, pp. 951-979 (2004) was published more than one year before the filing date of the '130 patent. DTX 01609. The Namaka reference was not disclosed by

Grünenthal and was not considered by the examiner during the prosecution of the '130 patent. *See* DTX 00075_0001 (Other Publications); *generally* PTX 01600.

4041. The Namaka reference summarizes the treatment options for physicians to treat neuropathic pain, including polyneuropathic pain. DTX 01609_0001, 0005. The full treatment algorithm is provided as Figure 2, which shows opioids as the second line treatment option for neuropathic pain. DTX 01609_0006; Brown 3/23/16 Tr. 18:18-24. The Namaka paper also discusses the evidence showing the efficacy of opioids (DTX 1609_0014-16) and is summarized in Table III. DTX 1609_0016. Specifically, the Namaka paper identifies studies showing the efficacy of the opioids morphine, methadone, and tramadol. DTX 1609_0014-16; Buvanendran 3/21/16 Tr. 64:1-4.

4042. Similarly, the reference Finnerup, Algorithm for neuropathic pain treatment: An evidence based proposal, *Pain*, Vol. 118, pp. 289-305 (2005) is another treatment algorithm published more than one year before the filing date of the '130 patent. PTX 1131. The Finnerup reference was not disclosed by Grünenthal and was not considered by the examiner during the prosecution of the '130 patent. *See* DTX 00075_0001 (Other Publications); *generally* PTX 01600.

4043. The Finnerup reference surveyed the available literature "as the basis of a proposal for an evidence-based treatment algorithm." PTX 1131 at JN_NUCYNTA_1634598. The Finnerup reference discusses the use of the opioids morphine, oxycodone, and tramadol for the treatment of polyneuropathic pain. PTX 1131 at JN_NUCYNTA_1634600; Buvanendran 3/21/16 Tr. 64:16-23, 65:1-5, 65:18-22. When synthesizing the evidence of all treatment options, the Freedman reference concludes that under any algorithm opioids are considered an effective treatment option for neuropathic pain. PTX 1131 at JN_NUCYNTA_1634603-04.

4044. The review article Freeman, The Treatment of Neuropathic Pain, *CNS Spectrums*, Vol. 10, No. 9, pp. 698-706 (2005) was published more than one year before the earliest filing date of the '130 patent. DTX 01603. The Freeman reference was not disclosed by Grünenthal and was not considered by the examiner during the prosecution of the '130 patent. *See* DTX 00075_0001 (Other Publications); *generally* PTX 01600.

4045. The Freeman article describes "the therapy of painful peripheral neuropathy in diabetes and post-herpetic neuralgia." DTX 01603_0003. Dr. Freeman includes a section regarding the use of opiates for the treatment of neuropathic pain. DTX 01603_0010-11. The Freeman article describes efficacy of opioids including tramadol (DTX 01603_0010; Buvanendran 3/21/16 Tr. 64:16-23) and multiple trials using oxycodone (DTX 01603_0011; Buvanendran 3/21/16 Tr. 64:24-65:5). Specifically, the Freeman article describes that the use of controlled release oxycodone can effectively treat diabetic neuropathy in a randomized, double-blind, placebo-controlled study. DTX 01603_0011.

4046. The article Baron, Diagnosis and Treatment of Neuropathic Pain, *Dtsch Arztebl*, Vol. 103, No. 41, pp. A 2720-30 (2006) was published before the earliest filing date of the '130 patent. DTX 01599. The Baron reference was not disclosed by Grünenthal and was not considered by the examiner during the prosecution of the '130 patent. *See* DTX 00075_0001 (Other Publications); *generally* PTX 01600.

4047. The Baron reference describes "a systematic review of the literature from the years 1980 to 2006" of clinical studies, meta-analyses, and the author's clinical experience. DTX 01599_0001. Table 2 of the Baron reference summarizes the quality of evidence for each of the treatment options, including the opiates tramadol, morphine, and oxycodone. DTX 01599_0007; Buvanendran 3/21/16 Tr. 64:16-23; Buvanendran 3/21/16 Tr. 64:24-65:5; Buvanendran 3/21/16

Tr. 65:14-22. According to the Baron reference, the literature review provided a well-founded basis for recommendation to use tramadol and oxycodone for peripheral nerve pain. DTX 01599_0007-08. Baron concludes, "with careful supervision, patients with chronic, non-malignant pain can be treated safely and effectively over long periods with strong opiates." DTX 01599_0008.

4048. The use of opioids for the treatment of polyneuropathic pain was not just confined to clinical studies; treating physicians were using opioids routinely to treat polyneuropathic pain. Buvanendran 3/21/16 Tr. 66:4-10. This commonly understood use of opioids was admitted in the specification of the '130 patent. The inventors wrote: "To treat neuropathic pain . . . ***morphine is also often used***, the range of side effects are which are, as is known, not without problems." DTX 00075_0002, 2:26-30 (emphasis added).

4049. When the art is considered as a whole, a POSA in March 2007 have been motivated to use tapentadol hydrochloride to treat polyneuropathic pain. Buvanendran 3/21/16 Tr. 68:1-23. A POSA in March 2007 would have considered it obvious to use a new opioid for the treatment of diabetic polyneuropathy. Buvanendran 3/21/16 Tr. 68:13-69:2. A POSA in March 2007 would have had a reasonable expectation of success that tapentadol would be effective in treating polyneuropathic pain. Buvanendran 3/21/16 Tr. 68:1-12.

4050. Dr. Brown discounted the published clinical evidence that opioids were effective in treating polyneuropathic pain because, in her opinion, there were concerns about side effects and patients' quality of life. Brown 3/23/16 Tr. 23:25-24:11. But the asserted claims are directed only toward treating polyneuropathic pain with tapentadol, not reducing side effects. Brown 3/23/16 Tr. 95:2-5. Additionally, Dr. Brown considered only the use of tapentadol in humans.

Brown 3/23/16 Tr. 106:20-25. This is because she is not an expert in animal models of pain. Brown 3/23/16 Tr. 48:14-16; *id.* 107:1-5

4051. Dr. Ossipov did not offer any opinions about the prior art use of opioids to treat polyneuropathic pain in the clinical setting. But in his opinion, a POSA would not have a reasonable expectation of success until he sees "information in a document that would show empirically that it treats polyneuropathic pain." Ossipov 3/23/16 Tr. 213:8-19.

4052. A POSA in March 2007 would have been motivated to test the efficacy of tapentadol in an animal model of polyneuropathic pain. Buvanendran 3/21/16 Tr. 69:3-9. And a POSA would have expected the results of the animal model to show efficacy for the treatment of polyneuropathic pain. Buvanendran 3/21/16 Tr. 69:10-11.

4053. During prosecution of the '130 patent, the examiner rejected the claims of the '130 patent as obvious in view of the '737 patent, the precursor to the '593 patent." PTX 1600 at Tab E (GRT-NUC00043876-82); Tab F (GRT-NUC00043980-84). The examiner rejected the claims because the '737 patent specification disclosed the "**treatment of severe pain.**" PTX 1600 at Tab F (GRT-NUC00043980 (emphasis in original)). In response, Grünenthal overcame the rejection by offering evidence of purported unexpected results presented in the declaration of Dr. Christoph. PTX 1600 at Tab G (GRT-NUC00044066-71); Tab H (GRT-NUC00044045-53).

4054. Dr. Brown offered no opinions regarding the conclusions of the patent examiners. This is because she did not consider Grünenthal's response to the rejections in view of the '737 patent from the prosecution history of the '130 patent. Brown 3/15/16 Tr. 73:16-20; *id.* 78:8-19; Brown 3/23/16 Tr. 83:25-85:20.

4055. Dr. Buvanendran did review the prosecution history, and agreed with the PTO that the '737 patent, which later became the '593 patent, renders the claims of the '130 patent

obvious. Buvanendran 3/21/16 Tr. 149:17-151:2 (discussing Tab E); *id.* 151:3-153:6 (discussing Tab F).

7. Plaintiffs did not present legally probative evidence of secondary considerations

4056. A POSA in March 2007 would have considered tramadol the closest prior art to tapentadol. Buvanendran 3/21/16 Tr. 71:6-9. Tramadol is the closest prior art to tapentadol because both are compounds with multiple mechanisms of action; both have a mu-opioid receptor component and a norepinephrine reuptake inhibition component. Buvanendran 3/21/16 Tr. 71:11-19; Christoph 3/14/16 PM Tr. 12:21-13:4.

4057. Plaintiffs did not offer any evidence comparing tapentadol to tramadol for the purposes of establishing an unexpected result. Specifically, Plaintiffs did not present any evidence that tapentadol has a superior side effect profile as compared to tramadol. Buvanendran 3/21/16 Tr. 71:24-72:1. Nor did Plaintiffs provide any evidence that tapentadol is more efficacious in treating polyneuropathic pain than tramadol. Buvanendran 3/21/16 Tr. 71:20-23.

4058. Because of the similar mechanisms of action, the data showing that tramadol was effective in treating polyneuropathic pain, such as diabetic polyneuropathy, would have created an expectation to a POSA in March 2007 that tapentadol would also be effective in treating polyneuropathic pain. Buvanendran 3/21/16 Tr. 72:2-10; DTX 01605_0002; DTX 01609_0015; DTX 01599_0008; DTX 00916_0007.

4059. The studies described in the Christoph declaration were comparing tapentadol with morphine, not a comparison to tramadol. PTX 1600 at Tab H; Christoph 3/14/16 PM Tr. 11:5-15; *id.* 12:7-20. But tramadol, not morphine, is the closest prior art to tapentadol. Buvanendran 3/21/16 Tr. 71:6-19; Christoph 3/14/16 PM Tr. 12:21-13:4. Dr. Brown agreed that it would not be fair to compare results of how tapentadol works versus morphine for

effectiveness in treating polyneuropathic pain. Brown 3/23/16 Tr. 98:12-16. Dr. Roush, Plaintiffs' chemistry expert, testified that tramadol and morphine and not in the same "galaxy" of mechanisms of action—the two are not equivalent comparators to tapentadol. Roush 3/22/16 PM Tr. 157:7-19.

4060. The only data presented by Plaintiffs directly comparing tapentadol and tramadol is in Table 3 of the '130 patent. DTX 00075_0007, 12:26-42. Even though the dose of tramadol was one third lower than the dose of tapentadol, it achieved almost identical results in the model of mechanical hyperalgesia. DTX 00075_0007, 12:26-42; Christoph 3/14/16 PM Tr. 25:3-22.

4061. Plaintiffs have not established what expectation of a person of the ordinary skill in the art would have had in March 2007 before attempting to use tapentadol to treat polyneuropathic pain in either animal models or the clinical setting.

4062. Based on the prior art establishing that opioids are effective in treating polyneuropathic pain, including diabetic polyneuropathy, a POSA would have expected that tapentadol would have been effective in the treatment of the same conditions. Buvanendran 3/21/16 Tr. 70:11-23; Buvanendran 3/21/16 Tr. 72:12-18; DTX 01605_0002; PTX 1141 at JN_NUCYNTA_1634622-23; DTX 01599_0007-08; DTX 01609_0014-16; PTX 1131 at JN_NUCYNTA_1634600, 1634603-04; DTX 01603_001011; DTX 01599_0007-08.

4063. Dr. Brown identified no expectation about the side effect profile of tapentadol before reading the package insert, not available until after the filing of the '130 patent. Brown 3/23/16 Tr. 93:2-19. Dr. Brown offers no opinion about what side effect profile a POSA would have expected for tapentadol in March 2007. *See id.* There are no "side effects . . . that are completely eliminated by using tapentadol as compared to tramadol." Brown 3/23/16 Tr. 92:23-93:1.

4064. Dr. Brown also testified that she had no opinion about what expectation a POSA would have had in March 2007 regarding the efficacy of tapentadol to treat polyneuropathic pain. Brown 3/23/16 Tr. 93:20-25.

4065. There was no long-felt need for additional treatment options for polyneuropathic pain in March 2007. Buvanendran 3/21/16 Tr. 72:21-73:9. In March 2007 the first-line treatment options for the treatment of polyneuropathic pain were antidepressants and antiepileptics. Buvanendran 3/21/16 Tr. 73:13-19; DTX 01603_0006; DTX 01609_0006 (Figure 2); PTX 1131 at JN_NUCYNTA_01634604. Opioids were a second-line treatment option for the treatment of polyneuropathic pain. Buvanendran 3/21/16 Tr. 73:20-25. E.g., DTX 01599_0007.

4066. The first-line treatment options available today are still tricyclic antidepressants and antiepileptics, and opioids are used as second-line treatments. Buvanendran 3/21/16 Tr. 74:1-6. Tapentadol is used as a second-line treatment option for polyneuropathic pain, just like other opioids. Buvanendran 3/21/16 Tr. 74:7-10. Dr. Brown agrees that tapentadol is not a first-line treatment for polyneuropathic pain. Brown 3/23/16 Tr. 89:4-16; Brown 3/15/16 Tr. 88:5-15.

4067. No head-to-head trials comparing tapentadol to the main treatments for polyneuropathic pain—gabapentin, pregabalin, TCAs or SNRIs—exist. DTX 00076_0005; Brown 3/23/16 Tr. 99:2-8. Dr. Brown testified that she did not know of evidence that would show whether tapentadol is superior to alternative treatments. Brown 3/23/16 Tr. 95:6-15.

4068. Independent reviews of tapentadol, published after its approval, indicate that tapentadol has not met any need in the market. The publication Veal and Peterson, Pain in the Frail or Elderly Patient: Does Tapentadol Have a Role?, *Drugs Aging*, Vol. 32, pp. 419-426 (2015), discusses the published clinical evidence regarding the use of tapentadol. DTX 00075.

4069. The authors identify as a "Key Point" that, "The evidence to support tapentadol is weak, with methodologically poor studies primarily sponsored by the drug company. Currently, there is insufficient evidence to support the use of tapentadol over other opioids, which have been on the market longer, are less expensive, and have better established safety profiles." DTX 00075_0001; *also* DTX 00075_0004 ("There are major limitations around the quantity and quality of clinical trials studying tapentadol."). The authors conclude in 2015 that, "[b]ased on the current evidence, tapentadol does not appear to provide any additional analgesic benefits compared to pre-existing therapies." DTX 00075_0006.

CONCLUSIONS OF LAW

I. U.S. PATENT RE39,593

1. The asserted claims of the ‘’593 patent are invalid as obvious under 35 U.S.C. § 103.

2. A POSITA, as of July 23, 1994, would have been motivated to select either tramadol or its metabolite *O*-desmethyltramadol as a lead compound for further development of an analgesic.

3. As of July 23, 1994, a POSITA would have understood that tramadol was unique among centrally acting strong analgesics.

4. A POSITA would have naturally selected tramadol and its metabolite *O*-desmethyltramadol as lead compounds for further modification in the search for new and improved analgesics.

5. A POSITA would want to maintain and/or enhance these “unique” and “atypical” activities in developing tramadol analogs.

6. A POSITA would have been motivated to develop tramadol analogs that maintained analgesic potency, but with reduced undesired side effects.

7. A POSITA would have been motivated to select the (+)/(–)-tramadol racemate, the (+)/(–)-*O*-desmethyltramadol racemate, or each of the individual stereoisomers (+)-tramadol, (–)-tramadol, (+)-*O*-desmethyltramadol, and (–)-*O*-desmethyltramadol as lead compounds, given the known contribution of each to the analgesic action of tramadol.

8. A POSITA would have known that the effects of both (+)-tramadol and (–)-*O*-desmethyltramadol were believed to consist of combined opioid and non-opioid components and would thus have a particular interest in the metabolite (–)-*O*-desmethyltramadol in order to avoid any complications associated with poor liver metabolism in certain patients.

9. In the search for improved analgesics with a mixed μ-opioid and non-opioid activity, among the individual stereoisomers of tramadol and *O*-desmethyltramadol, the prior art would have motivated a POSITA with experience in opioid analgesics to select (–)-*O*-desmethyltramadol as a lead compound for further development.

10. A POSITA would have considered only a finite number of modifications to tramadol or *O*-desmethyltramadol as promising when trying to improve its analgesic properties.

11. Based on the known structure-activity relationships of tramadol, a POSITA would have expected that certain structural aspects of tramadol known to be important for its analgesic activity (*i.e.*., the tramadol pharmacophore) would not be promising structural features for modification.

12. A POSITA would not be motivated to make a change to the dimethylaminomethyl group of tramadol or *O*-desmethyltramadol.

13. A POSITA would not be motivated to remove or alter the meta-hydroxy group (the O-Me group in the figure above) in tramadol or *O*-desmethyltramadol.

14. A POSITA would be motivated to design analogs of tramadol that have a meta-hydroxy group.

15. A POSITA would have been motivated to design tramadol analogs having the same stereochemical relationships as tramadol because this relationship between the phenyl ring and the dimethylamino side chain was known to be important for tramadol.

16. A POSITA having experience with opioid analgesics in July 1994 would have considered two features as most promising for possible modification that would reasonably lead to new compounds having similar or improved analgesic activity: these are the bridge-carbon hydroxyl group and the cyclohexane ring.

17. A POSITA would not have been motivated to esterify the bridge-carbon hydroxyl group, but would have been motivated to replace the bridge-carbon hydroxyl group of tramadol or *O*-desmethyltramadol with a hydrogen atom and would have had a reasonable expectation that the resulting compounds (shown below) would possess pharmacological activity, including analgesic activity.

18. A POSITA would not have expected that expanding or contracting the cyclohexane ring would have led to an analgesic compound with similar or improved properties compared to tramadol.

19. A POSITA would have expected that making more flexible analogs of tramadol would be an attractive option, because such compounds might reasonably be expected to adopt conformations that would enable optimal interactions, and thus enhanced binding, at both non-opioid and opioid receptors.

20. There are no surprising or unexpected results for tapentadol sufficient to establish nonobviousness of the asserted claims of the '593 patent.

A. The Asserted Claims Lack Utility Under 35 U.S.C. § 101 and § 112/1

501. "The utility requirement of 35 U.S.C. § 101 mandates that any patentable invention be useful and, accordingly, the subject matter of the claim must be operable." *In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1323-24 (Fed. Cir. 2009) (finding that "an invention that is simply an object of research" lacks utility). "If a patent claim fails to meet the utility requirement because it is not useful or operative, then it also fails to meet the how-to-use aspect of the enablement requirement [of § 112]." *Id.*

502. "Utility is a fact question." *Cross v. Iizuka*, 735 F.2d 1040, 1044 n. 7 (Fed. Cir. 1985).

503. A "patent may not be granted to an invention unless substantial and practical

utility for the invention has been discovered ***and disclosed.***" *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996).

504. Utility is determined as of the purported effective filing date, *Rasmusson v. SmithKline Beecham Corp.,* 413 F.3d 1318, 1323 (Fed. Cir. 2005), and based on how a POSA understands the asserted utility in the specification, *In re '318 Patent Infringement Litig.*, 583 F.3d at 1325-26.

505. In the chemical arts, to ascertain what the asserted utility is, a court asks what a POSA objectively understand the "***desired [pharmacological] response***" for the invention is based on what the specification discloses. *Fujikawa*, 93 F.3d at 1564 (emphasis added).

506. "It may be difficult to predict, however, whether a novel compound will exhibit pharmacological activity, ***even when the behavior of analogous compounds is known*** to those skilled in the art. Consequently, ***testing is often required to establish practical utility.***" *Fuijikawa*, 93 F.3d at 1564.

507. The testing disclosed in the specification must be '***reasonably indicative of the desired [pharmacological] response.***'" *Fuijikawa*, 93 F.3d at 1564 (italics in original.)

508. "[T]here must be a ***sufficient correlation*** between the tests and an asserted pharmacological activity so as to ***convince those skilled in the art***, to a ***reasonable probability***, that the novel compound will exhibit the asserted pharmacological behavior." *Id.* This determination is a "question of fact" based on whether "the test results as a whole were sufficient to establish pharmacological activity in the minds of those skilled in the art." *Id.* at 1566.

509. Utility may not be "inferred" from non-prior art compounds. *See Rasmusson*, 413 F.3d at 1324. "If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to

the likelihood of their success.'" *Id.* at 1325. Information that is not set forth in the patent specification may not support the asserted utility of a patent. *In re Brana*, 51 F.3d 1560, 1565 (Fed. Cir. 1995).

510. Post-filing data cannot generally be used to demonstrate the asserted utility. *In re '318 Patent Infringement Litig.*, 583 F.3d at 1325.

511. Only in limited circumstances, "a particular pharmacological activity identified with prior art compounds may have probative value as to the fact that the compound of the count possess this particular pharmacological activity where there is a structural similarity between the prior art compounds and the compound of the count." *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985); *see also Fujikawa*, 93 F.3d at 1565-66.

512. Two exceptions to the rule that post-filing data cannot be used to show the asserted utility are: 1) "[w]hen priority is not at issue;" and 2) when "post-filing evidence 'can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement ***already in the specification***." *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 925 (Fed. Cir. 2011) (emphasis added); *see also CreAgri, Inc. v. Pinnaclife, Inc.*, No. 11-cv-6635, 2013 U.S. Dist. LEXIS 179253, at *64 (N.D. Cal. Dec. 18, 2013) (Koh. J.).

513. When the asserted claims as originally filed lack utility, the patentee is not entitled to an earlier priority date based on that original application. *See Rasmusson*, 413 F.3d at 1323-24 (Fed. Cir. 2005).

514. Defendants have proven by clear and convincing evidence that claims 8, 61, 117, and 147 of the '593 patent are invalid for failure to satisfy the utility requirement because, based on the specification as originally filed, a POSA would not conclude that the claimed compounds have utility as analgesics without opioid side effects, enhanced analgesic properties compared to

tramadol, or merely efficacy as analgesics.

515. If post-filing data from the prosecution history is considered, then Defendants have proven by clear and convincing evidence that the earliest possible priority date for claims 8, 61, 117, and 147 of the '593 patent would be October 24, 2005.

B. Plaintiffs Did Not Rebut Obviousness As Of October 2005

516. Defendants have proven by clear and convincing evidence that, as of October 24, 2005, claims 8, 61, 117, and 147 of the '593 patent would have been obvious to a POSA, and thus invalid.

C. Claims 61, 117, and 147 Lack Written Description Under 35 U.S.C. § 112/1

517. A patent's specification must "contain a written description of the invention." 35 U.S.C. § 112.

518. The specification must "reasonably convey[] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

519. "[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a [POSA]." *Ariad Pharm. Inc., 598 F.3d* at 1351; *see also In re Smith*, 481 F.2d 910, 915 (C.C.P.A. 1973) (requiring that the "specification as a whole conveys possession . . . as of the filing date").

520. "[W]hether a patent complies with the written description requirement will necessarily vary depending on the context. Specifically the level of detail required . . . varies depending on the nature and scope of the claims and the complexity and predictability of the relevant technology." *Ariad Pharm. Inc.*, 598 F.3d at 1351 (citation omitted). There are no "bright-line rules governing, for example, the number of species that must be disclosed to describe a genus claim, as this number necessarily changes with each invention, and it changes

with progress in a field." *Id.*

521. Where the "record then features conflicting evidence about the reading a [POSA] would give [to the specification]," a finding that the specification lacks an adequate written description is appropriate. *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1345 (Fed. Cir. 2010) (emphasis added).

522. Defendants have proven by clear and convincing evidence that claims 61, 117, and 147 of the '593 patent are invalid for lack of adequate written description because the specification does not reasonably indicate to a POSA that the inventors possessed the subject matter of those claims.

523. Even if the prosecution history were to be considered, Defendants have proven by clear and convincing evidence that claims 61, 117, and 147 of the '593 patent are invalid for lack of adequate written description because the prosecution history does not reasonably indicate to a POSA that the inventors possessed the subject matter of those claims.

D. Claims 61, 117, and 147 Fail the Original Patent Rule Under 35 U.S.C. § 251(a)

524. A patentee is precluded from obtaining a reissue to any invention other than "the invention disclosed in the original patent." 35 U.S.C. § 251.

525. "[T]he ***[original parent] specification*** must ***clearly and unequivocally*** disclose the newly claimed invention as a separate invention." *Antares Pharma, Inc. v. Medac Pharma Inc.*, 771 F.3d 1354, 1362, 1363 (Fed. Cir. 2014) (emphasis added) (affirming a finding of invalidity because, even though the safety feature that was the subject of the later-added claims were described in the specification, "the ***particular*** combinations of safety features claimed on reissue [were not] disclosed in the specification").

526. A reissue application must find support in the original parent patent. *Id.*

527. The original "patent description [must] 'clearly allow persons *of* ordinary skill in the art to recognize that the inventor invented what is claimed.'" *Id.* at 1362. (internal quotation omitted).

528. "For § 251, 'it is not enough that an invention might have been claimed in the original patent because it was suggested or indicated in the specification.' Rather, the [original patent's] specification must clearly and unequivocally disclose the newly claimed invention as a separate invention." *Id.* (internal quotation omitted); *see also Goeddel v. Sugano*, 617 F.3d 1350, 1353 (Fed. Cir. 2010) (finding that because the application did not "describe[] or enable[] its practice in accordance with 35 U.S.C. § 112," it is not entitled to the earlier priotiy date in an interference proceeding).

529. Defendants have proven by clear and convincing evidence that claims 61, 117, and 147 of the '593 patent are invalid because they fail to satisfy the Original Patent Rule because the specification of the original '737 patent does not clearly and unequivocally disclose the inventions of claims 61, 117, and 147 of the '593 patent.

E. Genus Claim 8 Is Not Enabled Under 35 U.S.C. § 112/1

530. "Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue [*i.e.,* ***excessive***] experimentation." *Wyeth v. Abbott*, 720 F.3d 1380, 1384 (Fed. Cir. 2013) (emphasis added).

531. In *Wyeth*, the Court found that the claimed "rapamycin," which "may refer to a class of compounds," did not enable "the full scope of the claims [because it] would require ***synthesizing and screening each of at least tens of thousands of compounds.***" *Id.* at 1382, 1385 (italics in original) (emphasis added). "The resulting need to engage in a systematic screening process for ***each*** of the many rapamycin candidate compounds is excessive experimentation." *Id.* at 1386 (emphasis added).

532. The so-called *Wands* factors that may be considered in determining whether a disclosure would require undue experimentation include: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

533. Defendants have proven by clear and convincing evidence that claim 8 is invalid due to lack of enablement because practicing its full scope would require a POSA to engage in excessive, and thus undue, experimentation.

II. THE '364 PATENT

A. Anticipation of Claims 1-3 and 25

1001. Under 35 U.S.C. §§ 102 (a) and (b), "a [claim] limitation or the entire invention is inherent and in the public domain if it is the 'natural result[] flowing from' the explicit disclosure of the prior art." *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003) (quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001)); *see also Scaltech, Inc. v. Retec/Tetra, L.L.C.*, 269 F.3d 1321, 1329 (Fed. Cir. 2001).

1002. U.S. Patent No. 6,248,737 ("the '737 patent") which issued on June 19, 2001 and which reissued as Reissue Patent No. RE39,539, is a prior art reference for the '364 patent pursuant to 35 U.S.C. § 102(a) and (b).

1003. The asserted claims 1-3 and 25 of the '364 patent are invalid as anticipated because every limitation of the asserted claims is described in the '737 patent either expressly or inherently. *See* 35 U.S.C. § 102; *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1341 (Fed. Cir. 2011) (holding that a patent claim is not valid if each element is taught, whether expressly or inherently, in a single prior art reference).

1004. When considering whether the results of an experiment reproducing the prior art evidence inherent disclosure of the claimed invention, a key consideration is whether the "experiment . . . would . . . be considered by a chemist skilled in the art to be within the teaching of" the prior art. *Glaxo, Inc. v. Novopharm Ltd.,* 830 F.Supp. 871, 877 (E.D.N.C.1993), *aff'd,* 52 F.3d 1043 (Fed. Cir. 1995).

B. Obviousness of Claims 1-3 and 25

1005. Patented claims are invalid as obvious where "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a [POSA] to which said subject matter pertains." *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007).

1006. The obviousness inquiry requires that "the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are ascertained; and the level of ordinary skill in the pertinent art resolved." *KSR*, 550 U.S. at 406 (quoting *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966)).

1007. Obviousness is proven by showing that "'nothing more than routine' application of a well-known problem-solving strategy" was required to achieve the supposed invention. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368-69 (Fed. Cir. 2007) (citing *Merck & Co., Inc. v. Biocraft Labs, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989).

1008. Obviousness is determined as of the time of the invention, from the viewpoint of a hypothetical person or ordinary skill in the art. *In re Kotzab*, 217 F.3d 1365, 1369 (Fed. Cir. 2000): see *KSR*, 550 U.S. at 418. And the Supreme Court has emphasized, "[a] person or ordinary skill is also a person of ordinary creativity, not an automaton." *KSR*, 550 U.S. at 421.

1009. "Obviousness does not require absolute predictability of success," but, rather requires "a reasonable expectation of success." *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d

1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)). Obviousness "cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer v. Apotex*, 480 F.3d at 1364; see also *AstraZeneca LP v. Breath Ltd.*, 603 F. App'x 999 (Fed. Cir. 2015) (finding claims directed to budesonide compositions obvious, even though prior art did not disclose actual success because a POSA would have sufficient knowledge to address the uncertainty); *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186 (Fed. Cir. 2014) (known techniques rendered invention obvious, despite lack of absolute certainty for success); *In re Kubin*, 561 F.3d 1351, 1361 (Fed. Cir. 2009) (amount of acceptable unpredictability is greater in the natural sciences); *Hoffmann-La Roche, Inc v. Apotex, Inc.*, 2012 WL 1637736, at *16 (D.N.J. May 7, 2012) ("the law requires only a reasonable expectation" of success); *Warner Chilcott Co., LLC v. Teva Pharmaceuticals USA, Inc.*, 594 F. App'x 630, 636 (Fed. Cir. 2014) ("obviousness does not require absolute certainty or a guarantee of success."); *Purdue Pharmaceutical Products L.P. v. Actavis Elizabeth LLC*, 2015 WL 5032650, at *40 (D.N.J. Aug. 25, 2015); *Millennium Pharmaceuticals, Inc. v. Sandoz Inc.*, 2015 WL 4966438, at *4 (D. Del. Aug. 20, 2015); *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

1010. The Federal Circuit has recognized that, per *KSR*, evidence of a "finite number of identified, predictable solutions" or alternatives can "support an inference of obviousness." *See Eisai Co. Ltd. v. Dr. Reddy's Labs. Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008).

1011. A polymorph will be obvious where a starting compound is known; there is motivation to identify a polymorph of that compound; and the prior art contains illustrative instructions to generate the polymorph. See *in re Kubin*, 561 F.3d at 1360. The Federal Circuit in In re Kubin found obvious a claim directed to isolating and sequencing a human gene even

though the gene sequence was not in the prior art because the missing gene sequence could be identified and recovered "by standard biochemical methods." *Id*. at 1352, 1360-61. Accordingly, the Federal Circuit found the claimed invention was "the product not of innovation but of ordinary skill and common sense." *Id.* at 1360 (citing *KSR*, 550 U.S. at 421). This conclusion is all the more true where, as here, there are only two known polymorph options.

1012. Applying a well-known technique to a known pharmaceutical compound is obvious where a POSA would have had "within her toolbox" sufficient knowledge to address uncertainties. *See AstraZeneca*, 603 F. App'x at 1002. In *AstraZeneca*, for example, the Federal Circuit found invalid as obvious claims directed to sterile budesonide compositions, where the prior art disclosed non-sterile budesonide compositions and ordinary artisans were aware of five (5) sterilization techniques. 603 F. App'x at 1001-02. Even though each sterilization method could result in difficulties such as degradation, toxic residues, and agglomeration, this uncertainty could not save the claims from obviousness because "a skilled artisan had within her toolbox several methods to address them." *Id.* at 1002.

1013. Courts have found there is motivation in the pharmaceutical industry to "find and characterize new crystalline polymorphs." *E.g.*, *Merck & Cie, Bayer Pharma AG and Bayer Healthcare Pharmaceuticals Inc., v. Watson Laboratories, Inc.*, 125 F. Supp. 3d 503, 514 (D. Del. 2015); *In re Armodafinil Patent Litig.*, 939 F. Supp. 2d 456, 496 (D. Del. 2013).

1014. Each court that has declined to find polymorph screening renders polymorph patent claims invalid has lacked the benefit of the Byrn article, or any article that evidences how the patentee followed the specific and express teachings of the prior art including a limited and finite set of solvents and a flowchart to guide selection of conditions. See *Merck*, 125 F. Supp.

3d at 514. Merck, for example, cited no prior art guidance to illustrate a polymorph screen. 125 F. Supp. 3d at 514.

1015. In light of the compound disclosed in the '737 patent, industry motivation to perform a polymorph screen, and commonly known polymorph screening techniques, a polymorph generated by following the specific guidance of the Byrn article is ineligible for patenting because the prior art discloses (1) the compound; (2) a motivation to identify a polymorph of that compound; and (3) illustrative instructions to generate the polymorph. *See in re Kubin*, 561 F.3d at 1360.

1016. Claims 1-3 and 25 of the '364 patent are invalid pursuant to 35 U.S.C. § 103 as obvious in light of the '737 patent and knowledge commonly available to a POSA pertaining to polymorph screening.

C. Lack of Utility

2001. The legal standard for lack of utility is summarized in paragraphs 501 to 509 above.

2002. The patentee is required to show that its invention has "characteristics or qualities of utility that are new and materially different from [that] disclosed by the art of record." *Application of Selmi*, 156 F.2d 96, 99 (C.C.P.A. 1946) (citing *Dow Chemical Co. v. Halliburton Oil Well Cementing Co.*, 324 U.S. 320 (1945)).

2003. There must be a "specific allegation of utility for any compound within the scope of the claims." *In re Kirk*, 375 F.2d 940, 942 (C.C.P.A. 1967) (finding that there was a lack of adequate utility for "a steroid chemical compound" because a POSA would not know "'how to use it' simply because the compound is closely related only in a structural sense to other steroid compounds known to be useful). "[A]n application must disclose a use which is not so vague as to be meaningless." *In re Fisher*, 421 F.3d 1365, 1372, 1377 (Fed. Cir. 2005) (holding that the

"laundry list of uses, like the terms 'biological activity' or 'biological properties' . . . are nebulous, especially in the absence of any data demonstrating that the claimed ESTs [expressed sequence tags, or purified nucleic acid sequences] were actually put to the alleged uses").

2004. Where there is "'no indication that one skilled in the art would accept without question statements as to the [asserted] effects . . . and no evidence has been presented to demonstrate that the claimed products do have those effects,' an applicant has failed to demonstrate sufficient utility[.]" *Rasmusson*, 413 F.3d at 1323.

2005. A process for making a product that has not yet itself been shown to be useful cannot meet the utility requirement. *See Brenner v. Manson*, 383 U.S. 519, 534 (1966) (finding that a claim for a process to make a steroid lacked utility when there was no disclosure of the use for the specific steroid made by the process and that the chemical process yielded the intended product was insufficient).

2006. Defendants proved by clear and convincing evidence that the '364 patent specification lacks utility because the statement of utility is inherently vague and insufficient; and even assuming that the specification's statement were clear, a POSA reading the specification would not find that there was sufficient disclosure to support that asserted utility.

D. Unclean Hands

2007. A court of equity may dismiss a cause of action "where some unconscionable act of one coming for relief has immediate and necessary relation to the equity that he seeks in respect of the matter in litigation." *Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933). "Any willful act concerning the cause of action which rightfully can be said to transgress equitable standards of conduct is sufficient cause for the invocation." *Precision Instrument Mfg. Co. v. Auto. Maintenance Mach. Co.*, 324 U.S. 806, 815 (1945); *see also Hazel-Atlas Glass Co. v. Hartford-Empire Co.*, 322 U.S. 238, 240 (1944) (In an effort to overcome an

"insurmountable Patent Office opposition," patentees had to manufacture a false article praising the invention "as a remarkable advance in the art.").

2008. In the patent context, the doctrine of unclean hands may render a patent unenforceable by a patentee who has engaged in misconduct in practicing before the PTO. *Therasense, Inc. v. Becton, Dickinson & Co*., 649 F.3d 1276, 1306-07 (Fed. Cir. 2011). For example, in *Monsanto Co. v. Rohm & Haas Co*., 456 F.2d 592, 595 (3d Cir. 1972), the Court affirmed the district court's finding that "Monsanto intentionally withheld material facts in order to mislead the Patent Office, thereby making its application for patent taken as a whole misleading [and] that Monsanto came into court with unclean hands."

2009. "Because direct evidence of deceptive intent is rare, a district court may infer intent from indirect and circumstantial evidence." *Therasense*, 649 F.3d at 1290. "Bad faith may be established by circumstantial evidence and each case must depend upon its peculiar facts." *Bankers Trust Co. of Western N.Y. v. Crawford*, 781 F.2d 39, 44 (3d Cir. 1986); *see also Ohio Willow Wood Co. v. Alps S., LLC*, 813 F.3d 1350, 1359 (Fed. Cir. 2016) (inferring deceptive intent from misrepresentations to the PTO and withholding pertinent information); *Monsanto Co.*, 456 F.2d at 599 (emphasis added) ("[A]n examination of the report permits, if not compels, the misleading ***inference*** that it constituted a complete and accurate analysis of all the testing instead of an edited version thereof [and that c]oncealment and nondisclosure may be 'evidence and equivalent to a false representation, because the concealment or suppression is, in effect, a representation that what is disclosed is the whole truth'").

2010. Grünenthal acted with unclean hands and thus rendered the '364 patent unenforceable against Defendants when it engaged in misconduct in practicing before the PTO and that unconscionable act had immediate and necessary relation to the equity that Plaintiffs

now seek.

[redacted]

[redacted]

[redacted]

B. The Claims of the '130 Patent are Invalid as Anticipated

3501. The claims if the '130 patent are invalid as anticipated under 35 U.S.C. 102(b) because the '737 patent inherently anticipates the claims of the '130 patent.

3502. U.S. Patent No. 6,248,737 ("the '737 patent") issued on June 19, 2001, more than one year before the filing of the earliest application to which the claims of the '130 patent may claim priority and is prior art to the claims of the '130 patent under 35 U.S.C. § 102(b).

3503. Example 25 of the '737 patent discloses tapentadol hydrochloride, and describes it and related compounds as being "suitable for the treatment of severe pain."

3504. Although the '737 patent does not expressly state that some of the population with severe pain will suffer from polyneuropathic pain, it is necessarily true that some severe pain sufferers have polyneuropathic pain..

3505. The same method and purpose recited in the claims of the '130 patent are described in the '737 patent, namely administering tapentadol hydrochloride to treat pain, and the population in the '737 patent (those with "severe pain") includes the subgroup of those with polyneuropathic pain.

C. Obviousness-type Double Patenting

4001. The judicially-created doctrine of obviousness-type double patenting ("OTDP") exists to prevent a patentee from securing a second patent on the same or obvious variation of a previously issued patent claim, and thus improperly extending the exclusionary right. *Abbvie Inc. v. Mathilda & Terence Kennedy Institute of Rheumatology Trust*, 764 F.3d 1366, 1373–74 (Fed. Cir. 2014).

4002. OTDP is analyzed by first construing the two claims, then determining whether the differences between the earlier and later claim render the later-issued claim patentably distinct from the earlier-issued claim. *Id.* at 1374. The relevant time frame for determining

OTDP is the filing date of the later-issues patent (i.e., March 2007), so a POSA gets to consider the developments in the art between the filing of the '593 and the '130 patents. *Amgen Inc. v. Hoffman-LaRoche Ltd.*, 580 F.3d 1340, 1355 (Fed. Cir. 2009) (discussing *Takeda Pharm Co. v. Doll*, 561 F.3d 1372 (Fed. Cir. 2009)).

4003. A later-issued claim is obvious "where an earlier patent claimed a compound, disclosing its utility in the specification, and a later patent claimed a method of using the compound for a use described in the specification of the earlier patent." *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010); *see also Ariad*, 764 F.3d at 1379 (later-claimed species are unpatentable for OTDP when earlier-disclosed genus allows POSA to envision every member of the class).

4004. Thus, claim 117 of the '593 patent renders obvious the claims of the '130 patent.

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Respectfully submitted,

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CERTIFICATION OF SERVICE

I hereby certify that on April 18, 2016, a copy of the foregoing DEFENDANTS' PROPOSED FINDINGS OF FACT AND CONCLUSIONS OF LAW was served by notice of electronic filing and electronic mail upon all counsel of record.

_____James S. Richter_____